DEFERIPRONE EVALUATION IN PAEDIATRICS

Multicentre, randomised, open label, non-inferiority active-controlled trial to evaluate the efficacy and safety of deferiprone compared to deferasirox in paediatric patients aged from 1 month to less than 18 years affected by transfusion dependent haemoglobinopathies.

Product	**DEFERIPRONE**
Protocol No.	**DEEP-2**
EudraCT No.	**2012-000353-31**
Phase	**III**
Sponsor	**Consorzio per Valutazioni Biologiche e Farmacologiche** Via Luigi Porta 14 – 27100 Pavia - ITALY
Sponsor's Legal Representative	**Dr. Donato Bonifazi** Consorzio per Valutazioni Biologiche e Farmacologiche Via Luigi Porta 14 – 27100 Pavia - ITALY
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Funder	**European Commission** (FP7 Framework Research program "HEALTH-2010.4.2-1: Off-patent medicines for children")
Version	4.0
Release date	10 December 2015

Summary of Relevant Changes to DEEP-2 Protocol

Version 3.0 (release date 10 February 2015) to version 4.0 (release date 10 December 2015).

A summary of the key changes incorporated into DEEP-2 Protocol version 4.0 is provided below.

*1. Section 5.1 "Inclusion Criteria": as new PK/dosing data of deferiprone in this age group (Study DEEP-1, EudraCT n. 2012-000658-67) are available, the inclusion criterion "*for patients aged from 1 month to less than 6 years: known intolerance or contraindication to DFO*" has been modified in order to allow children aged from 1 month to less than 6 years without known intolerance or contraindication to deferoxamine to be included in this study.*

2. Section 4 "Study design", Section 5 "Selection and enrolment of subjects" and Section 11.12 "Sample size and power considerations": the dropout rate has been increased from 10% to 20% according to a reliable evaluation of the percentage of patients able to complete the study.

3. Table 4. "Serum Creatinine" and "Urinalysis", footnote 5 of table 5, paragraphs 7.3.15 "Urinalysis" and 7.3.16 "Renal Function": the frequency of the assessment [weekly (± 7 days) during the first month after initiation or modification of therapy] has been revised.

SIGNATURE PAGE

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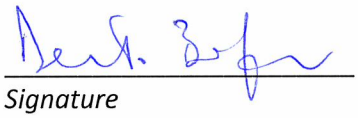

Signature

10/12/2015
Date of Signature

Investigators Protocol Agreement Page

Coordinating Investigator
I acknowledge that I am responsible for overall study conduct.

I agree to personally conduct or supervise the described clinical study.

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Principal Investigator
I confirm agreement to conduct the study in compliance with the protocol, the Good Clinical Practice (GCP), all applicable subject privacy requirements including EU[1] and local regulations, and the guiding principles of the 2008 Helsinki Declaration.
I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Name: _____ **Site Number**: _____

_____ _____

Signature *Date of Signature*

_____

[1] In Europe the principles of the protection of the rights and freedoms of individuals, notably the right to privacy, are contained in the Article 8 of the **European Convention for the Protection of Human Rights and Fundamental Freedoms**[1], the Convention of 28 January 1981 for the Protection of Individuals with regard to Automatic Processing of Personal Data[1], the Directive 95/46/EC[1] and in the general principles of EU law.

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AE	Adverse Event
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
CHQ	Child Health Questionnaire
CRF	Case Report Form
DFO	Deferoxamine
DFP	Deferiprone
DFX	Deferasirox
dL	decilitre
DSMC	Data Safety Monitoring Committee
dw	dry weight
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
Fe	Iron
GCP	Good Clinical Practice
GEE	Generalised Estimating Equations
GI	gastrointestinal
Hb	Haemoglobin
HRQoL	Health Related Quality of Life
IEC	Indipendent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent To treat
L	litre
LIC	Liver Iron Concentration
MAH	Marketing Authorization Holder
mg	milligram
ms	milliseconds
PDCO	Paediatric Committee
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PP	Per Protocol
QoL	Quality of Life
QPPV	Qualified Person for PharmacoVigilance
REB	Research Ethics Board
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Safety Contact
SCD	Sickle Cell Disease
SID	Study Identification Number
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
UAR	Unexpected Adverse Reaction
WBC	White Blood Cells
WHO	World Health Organization

1. PROTOCOL NUMBER

This study is being conducted under protocol number: **DEEP-2**

EudraCT number: **2012-000353-31**

2. OBJECTIVES

2.1Primary Objective

The primary objective of this study is to assess the non-inferiority of deferiprone (DFP) compared to deferasirox (DFX) in terms of changes of ferritin levels and heart iron concentration in paediatric patients affected by hereditary haemoglobinopaties requiring chronic transfusions and chelation.

2.2Secondary objectives

Secondary objectives of this study are:

- to assess treatment efficacy in terms of ferritin levels
- to assess treatment efficacy in terms of cardiac MRI T2* in patients over 10 years of age able to perform MRI scan without sedation
- to estimate the efficacy of treatments in terms of liver iron concentration (LIC) measured by MRI in all paediatric subjects able to have MRI scan without sedation
- to evaluate the safety and tolerability profile of treatments
- to assess healthcare resources utilisation and patient global assessment, including compliance and quality of life (QoL) evaluation
- to confirm the influence of demographic covariates on the pharmacokinetic disposition of treatments across the study population.

2.3Exploratory objectives

Additional and exploratory objectives of the study include the assessment of the correlation between systemic exposure to the investigational drugs and serum ferritin levels observed after one year treatment.

3. BACKGROUND

3.1Condition

Haemoglobinopathies are a group of inherited disorders characterized by structural variations of the haemoglobin molecule which often lead to ineffective erythropoiesis. Frequent blood transfusions are the recommended treatment to suppress ineffective erythropoiesis and to provide adequate oxygen carrying capacity. Patients become iron overloaded within 3 to 24 months of a transfusion regimen aimed to maintain a minimum haemoglobin (Hb) concentration of 9.5 to 10.5 g/dL.

Examples of transfusion-dependent anaemias include aplastic anaemia, Diamond-Blackfan anaemia (red blood cell aplasia), dyserythropoietic anaemias, Fanconi anemia (hypoplastic anaemia), myelodysplastic syndromes, sickle cell disease (SCD) and thalassaemia major. Some of these anaemias are genetic, start

early in the life and affect children as well as adults. Hereditary haemoglobinopathies such as thalassemia major and SCD are the most representative in this group.

This study will include **hereditary haemoglobinopathies requiring chronic transfusion therapy, including but not limited to thalassemia syndromes and sickle cell disease (SCD).**

Unfortunately, all chronically transfused patients become clinically iron overloaded as there is no physiological mechanism for the removal of the excess of transfused iron from the body.

The pathologic changes and clinical manifestations associated to chronic iron overload are common among all chronically transfused patients, albeit best documented in patients with thalassemia major. In the most severe forms of transfusion-dependent anaemia, after only few years on regular transfusion regimen, the iron storage capacity of the liver and other organs (heart and endocrine organs) is exceeded, thus leading, in the absence of adequate intervention, to the development of a multi-system organ dysfunction. For example in thalassemic patients, it has been demonstrated that, after the age of 8-10 years, patients are at risk of developing severe complications related to iron accumulation, i.e. growth retardation, with 25% to 60% of patients being reported below the third percentile of height (Gabutti V and Piga A, 1996; Cappellini MD et al., 2008). Arrested puberty, reported in 38-80% of males and 30-70% of females, is also a relatively common complication in moderately or grossly iron overloaded patients with thalassaemia, and is characterised by a lack of pubertal progression over a year or more leading to failure or delay of sexual maturation (Gabutti V and Piga A, 1996).

Iron overload may be prevented or treated with chelating agents capable of complexing with iron and promoting its excretion. The introduction of chelation therapy combined with the regular transfusions since the early 1980s, has changed radically the clinical history of thalassaemia and other hereditary haemoglobinopathies, leading to a significant survival increase and to a relevant improvement in the patients QoL (Borgna-Pignatti C et al., 2006; Ceci A et al., 2006).

In the current clinical practice iron chelating treatment in thalassaemia major patients starts when serum ferritin levels reach about 1000 μg/L, which usually occurs after 10-20 blood transfusions when the patient can be on average 2 or 3 year old or less depending from the amount of transfused red blood cells.

The first chelating agent approved for clinical use was deferoxamine (DFO) which has played a central role in the iron overload treatment.

Deferoxamine treatment has satisfactory therapeutic effects, but the prognosis remains poor because its requirement for prolonged subcutaneous infusion make the drug too burdensome for full adherence, thus leading to poor or non-compliance in a high percentage of patients, particularly in the paediatric population (Giardina PJ et al., 2001). Moreover, 10-15% of subjects are unable to use this chelator due to hypersensitivity or toxic side effects.

Starting from these considerations, in the recent years many oral compounds have been studied. Research has led to the identification of several interesting molecules but, among these, only two agents became available on the European Market: deferiprone and deferasirox.

Deferiprone (DFP, Ferriprox®) is the first oral iron chelating agent introduced in Europe. It was authorised by the European Medicines Agency (EMA) in 1999 for the treatment of patients with thalassaemia major when DFO therapy is contraindicated or inadequate. Initially, the MA was granted on the basis of evidence collected in small clinical studies. However, later controversies regarding DFP safety and efficacy prompted the appropriate investigation of its use in large post-marketing surveillance programs where data from over 6000 patients using DFP in some case for more than 10 years, have been collected (Ceci A et al., 2002; al-Rafaie FN et al., 1994; Taher A et al., 2001; Olivieri NF et al., 1997; Ceci A et al, 2011). Recently the EMA has

updated the Summary of Product Characteristics (SmPC) including the statement that "DFP demonstrated to be superior to DFO in decreasing cardiac iron load" (Ferriprox® SmPC 2010).

However, despite wide experience of DFP in patients with iron overload (specifically thalassaemic) limited data are available for younger children. Thus, due to a lack of data submitted to the Regulatory agency from comparative studies, the drug is still approved only for second line treatment. Consequently, the need for additional data on DFP was expressly included by the PDCO (the Paediatric Committee at the EMA) in the 2009 PDCO Priority List and an independent research Consortium (DEEP- Deferiprone Evaluation in Paediatrics) has been set up and funded by the European Commission under the FP7 Framework Research program "HEALTH-2010.4.2-1: Off-patent medicines for children".

Deferasirox (DFX, Exjade®) the second approved oral chelator, is a once-daily orally active iron chelator, firstly introduced in USA, and authorised in Europe under the Centralised Procedure for treating chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major above 6 years of age and in patients under 6 years of age when DFO therapy is contraindicated. The safety and efficacy profile of DFX was compared with DFO, and non-inferiority to this drug was demonstrated in patients with LIC ≥ 7 mg Fe/g dw. Post marketing long-term data have identified renal impairment as a safety risk associated with DFX therapy in both paediatric and adult patients and consequently the SmPC has been updated accordingly (Annex 1). Nevertheless, DFX with its PK profile allowing the maintenance of plasma levels within the therapeutic range for 24-hour period, and permitting once-daily oral administration, is currently the most widely used chelator in the paediatric subset (Ceci A et al., 2011).

3.2 Study population

The present study will include all the hereditary haemoglobinopathies (including but not limited to thalassaemia syndromes and SCD) that affect the paediatric population from 1 month to less than 18 years of age and requiring frequent transfusions (at least 150 ml/kg/year of packed red blood cells corresponding approximately to 12 transfusions) and chelation. Chelation naïve patients will be included if they have received at least a quantity of 150 ml of packed red blood cells/kg corresponding to approximately 12 blood transfusions.

3.3Interventional drugs

Deferiprone is the experimental drug.

Deferiprone will be administered orally at the approved dosage of 75-100mg/kg/day for 7 days per week for the entire duration of the treatment (12 months).

For children from 1 month to less than 6 years, where limited data are available in the SmPC and in literature, the dosage will be derived by the results of an *ad hoc* designed Pharmacokinetic (PK) study sponsored by the same DEEP Consortium (Study DEEP-1, EudraCT n. 2012-000658-67).

The deferiprone formulation to be used in this trial is a new strength (80 mg/mL) of the currently marketed DFP oral solution (Ferriprox® 100 mg/mL oral solution), with some changes in excipients. This lower strength formulation was recently developed by the Marketing Authorisation Holder (MAH) and included in an approved Paediatric Investigational Plan (PIP), and will allow the administration of more accurate volumes in children, minimising the risk of over- or under-dosing. This formulation will also provide the advantage of improved palatability, thus ameliorating objections to the inherently bitter taste of the currently available syrup. Thus, it is expected to improve patients' compliance, and thereby clinical outcomes and quality of life (QoL). For further details please refer to **Section 6.1**.

Deferasirox (Exjade®) is the comparator.

DFX dosage will range from 20 to 40 mg/kg/day as recommended in the SmPC currently approved in Europe (**Annex 1)**. For further details please refer to **Section 6.2.**

4. STUDY DESIGN

This is a Phase III study, providing efficacy and safety data after one year treatment with DFP and DFX.

No studies directly comparing DFP and DFX are available. Published literature including the most recent meta-analyses (Roberts D et al, 2007; Maggio A et al, 2010; Meerpohl JJ et al, 2012) compares the efficacy of both IMPs with that of DFO and demonstrate that their efficacy profiles are non inferior to those of DFO. These findings refer mainly to adults but include also some data in the paediatric population. On this basis testing for non-inferiority of DFP versus DFX is well supported.

Thus, this study has been designed as a multicentre, randomized, open label, active comparator controlled, parallel group trial for establishing the non-inferiority of DPF to DFX in terms of changes in ferritin levels and cardiac iron concentration in paediatric patients after 1 year of treatment.

Evidence that serum ferritin is a reliable parameter to evaluate any chelator efficacy has been widely published (Gabutti V and Piga A. 1996; Olivieri, N. et al 1994; Telfer PT, 2000; Borgna-Pignatti, 2004) and represents the basis for monitoring therapy and assessing efficacy particularly in the paediatric population.

However, more recent literature highlights also the important role of cardiac MRI T2* in the understanding and treatment of cardiac siderosis. In the paediatric population iron accumulation in the heart begins to be evident later than in the liver and evidence has been accumulating suggesting that the use of MRI T2* is not of value in chelated patients prior to about 10 years of blood transfusions (Wood JC, 2008, Meloni A., HTA-Thal project funded by Italian Ministry of Health, final project meeting, Rome, June 28, 2011; Guidelines for the clinical management of Thalassaemia, 2nd revised edition, Thalassaemia International Federation, 2008). Moreover, cardiac MRI T2* evaluation has limited application to younger patients unable to undergo the scan without being sedated. For the above mentioned reasons, the performance of a cardiac T2* in children over 10 years is generally recommended in clinical practice, unless clinical condition suggests a cardiac evaluation before that age.

On such evidence, treatment efficacy will be measured in terms of percentage of successfully chelated patients assessed with ferritin and cardiac MRI T2* as defined in **Section 4.3**.

The target patient population consists of 388 outpatients affected by hereditary haemoglobinopathies requiring chronic transfusion and chelation, randomized 1:1 in two groups of 194 patients each to ensure 310 evaluable patients. Chelation naïve and not naïve patients aged from 1 month to less than 18 years will be recruited. A staggered approach will be applied to patients aged less than 6 years (10% of the total sample), which will be recruited after results from the PK Study (Study DEEP-1, EudraCT n. 2012-000658-67) will be available.

Experimental arm: patients administered with DFP at 75-100 mg/kg/day for seven days per week. In patients aged less than 6 years the dose will be defined according to the results of the PK Study (Study DEEP-1, EudraCT n. 2012-000658-67). DFP daily dose will not exceed 100 mg/kg.

Control arm: patients administered with DFX at 20-40 mg/kg/day as recommended by the currently approved European SmPC (last update 10/08/2011). DFX daily dose will not exceed 40 mg/kg.

Details on the starting dose and subsequent dose adjustments are reported in **Section** 6**.**

The **treatment duration** for both groups is 12 months.

4.1Non-inferiority margin

This study is designed to demonstrate the **non-inferiority** of a new liquid DFP (80 mg/mL) formulation in comparison with DFX in terms of percentage of successfully chelated patients as described in **Section 4.3**.

DFP will be declared non inferior to DFX if the lower limit of the 95% confidence interval for the difference in the proportion of successful chelation in the two groups is above -12.5%. The choice of this margin is based on clinical considerations starting from the available evidences for the effects of DFX at both ferritin and cardiac levels. For details please refer to **Section 11**.

4.2Choice of comparator

DFP will be compared to the oral chelating agent DFX. The rationale for comparing two oral chelators derives from the recent literature data reporting that oral chelating agents currently represent the most widespread adopted therapy in the paediatric age, due to good compliance, improved QoL and reduced burden of the disease (Ceci A et al, 2011).

4.3Primary endpoint

The primary endpoint will be the measure of treatment efficacy defined as the percentage of patients successfully chelated, as assessed by serum ferritin levels (in all patients) and cardiac MRI T2* (in patients above 10 years of age able to have an MRI scan without sedation).

In details, a composite outcome measure will be defined as primary endpoint of the study according to patient's age, as follows:

- in patients < 10 years of age treatment success will be defined only in terms of serum ferritin level (criterion A);
- in patients ≥ 10 years of age treatment success will be defined in terms of both serum ferritin level and cardiac MRI T2* (criteria A and B).

In patients ≥10 years of age who would require sedation for the MRI scan, treatment success will be defined only in terms of serum ferritin level (criterion A). Details on the choice of the composite outcome are in **Section 11.1.**

4.3.1 Definition of successful chelation

The following criteria will be used to identify a treatment success:

A. Criterion A - Serum Ferritin Levels: success for patients with baseline serum ferritin levels of 2500 ng/mL or more will be defined as a 20% reduction or more after 1 year treatment. Success for patients with baseline serum ferritin levels less than 2500 ng/mL will be defined as any decrease in serum ferritin, or an increase in serum ferritin, if that increase is less than or equal to 15% of the baseline level, as long as the increase does not result in a serum ferritin above 2500 ng/mL within 12 months despite continual transfusional therapy.

B. Criterion B - MRI T2* Cardiac Iron Concentration: success for patients with baseline values of 20 ms or more will be defined as any increase in T2* or, if there is a decrease, the decline is not more than 10% after 1 year, as long as this does not results in a value below 20 ms. Success in patients with a baseline less than 20 ms will be defined as an increase in T2* of 10% or more despite transfusional therapy.

Table 1 summarises the applied criteria.

Table 1. Definition of treatment success

Baseline ferritin ≥ 2500 ng/mL	Reduction of 20% or more after 1 year treatment
Baseline ferritin < 2500 ng/mL	• any decrease • increase ≤ 15% as long as the increase doesn't result in ferritin > 2500 ng/ml after 1 year treatment

Baseline MRI T2* < 20 ms	Increase of 10% or more after 1 year treatment
Baseline MRI T2* ≥ 20 ms	• any increase • decrease ≤ 10% after 1 year treatment as long as the decrease does not result in MRI T2* value < 20 ms

4.4Secondary endpoints

4.4.1 Serum ferritin levels

Serum ferritin levels will be evaluated as secondary endpoint and will be measured in the entire patient population. It is a well validated and clinically accepted surrogate measure of iron load, correlated with LIC, and easily assessed in the paediatric population.

Quarterly blood sampling for ferritin measure is planned both at local and central laboratory/ies level during the 1 year treatment. All formal analyses will be based upon values generated in the central laboratory/ies.

Serum ferritin, as a component of the composite endpoint, will be analysed as secondary endpoint with the intent of clarifying the interpretation of the composite and finally supporting treatment efficacy (Turk DC et al, 2008). Non inferiority of DFP to DFX will be established using ferritin as continuous variable.

In addition, serum ferritin trends over time will be compared to investigate potential difference between DFP and DFX treatments. Details of the analyses are reported in **Section 11.2**.

4.4.2 Cardiac MRI T2*

Cardiac MRI T2* will be evaluated as secondary endpoint and will be measured in patients aged 10 years or more and able to undergo the evaluation without being sedated.

Cardiac iron load will be assessed - adopting the Cardiac MRI T2*-based technology and protocol from Resonance Health Ltd. - at baseline, and after 6 and 12 months of treatment.

Cardiac MRI T2*, as a component of the composite endpoint, will be analysed as secondary endpoint with the intent of clarifying the interpretation of the composite (Turk DC et al, 2008). Cardiac MRI T2* will be analysed as a binary variable (with success defined as in **Section 4.3.1**, criterion B). Additional details on the analysis are reported in **Section 11.2** and **Section 11.4**.

4.4.3 Liver MRI

The efficacy of treatment in terms of LIC as measured by MRI will be a secondary endpoint and will be assessed in all patients able to undergo MRI scan without sedation.

Liver MRI will be assessed - adopting the Ferriscan® technology and protocol from Resonance Health Ltd. - at baseline and after 12 months of treatment.

Efficacy will be assessed in terms of percentage of successfully chelated patients. The criterion for success has been differently defined according to a threshold for baseline LIC. Success for patients with values of 7 mg/g dry weight or more will be defined as a reduction by 20% or more after 1 year treatment. Success for patients with a baseline less than 7 mg/g dry weight will be defined as a decrease in LIC, or if there is an increase in LIC, it will not be more than 15% after 1 year treatment despite continued transfusion with chelation therapy (**Table 2**).

Table 2. Definition of treatment success for liver MRI

Baseline LIC ≥ 7 mg/g dry weight	Reduction of 20% or more after 1 year treatment
Baseline LIC < 7 mg/g dry weight	Decrease in LIC or an increase ≤ 15% after 1 year treatment as long as the increase does not result in a LIC value > 7 mg/g dry weight

4.4.4 Safety and tolerability

Safety and tolerability assessments will consists of monitoring and recording all Adverse Events (AE) and Serious Adverse Events (SAE) as defined in **Section 16.1**, regular monitoring of haematology, blood chemistry and urine values, regular measurements of vital signs, performance of physical examinations, standard measures of growth and maturation.

4.4.5 Pharmacokinetics

Plasma samples will be collected at the end of treatment for the assessment of drug concentrations at steady-state conditions in all the patients until a patients' number leading to statistically significant analysis is reached. Pharmacokinetic data will then be analysed to confirm the influence of relevant covariates (e.g., demographics) on the systemic exposure to drug treatments.

4.4.6 Healthcare Resources Utilisation

At each scheduled monthly visit the level of health care resources utilization in the previous month will be recorded. Specifically, the frequency and duration of inpatient hospitalization related to patient haemoglobinopathy will be recorded along with the primary reason for the hospitalization. For each hospitalization the duration spent in each of the following will be recorded: ICU, general ward, emergency room, other. Hospitalizations will be defined as any visit to the hospital requiring an overnight stay. The frequency of outpatient visits will be recorded along with the type of physician the patient saw and the type of visit. An outpatient visit will be defined as any visit to a medical practitioner or to a specialist not requiring an overnight stay. Any resource used in addition to those foreseen in the protocol will be recorded.

4.4.7 Compliance

Compliance to treatment will be assessed by evaluating the DFP solution volume in each medicine bottle or the number of DFX dispersible tablets in the blister pack remaining at each visit.

DFP used volume will be evaluated measuring the difference between the intact bottle volume (250 ml) and the remaining volume in the returned bottle.

4.4.8 Quality of Life

Child Health Questionnaire™ (CHQ) will be assessed to evaluate the Health Related Quality of Life (HRQoL) from the point of view of parents or guardians. CHQ is 28 items generic quality of life instrument designed and normed for children 5-to-18 years of age (**Annex 2**).

CHQ will be completed at baseline, at month 6 (V9) and after 12 month of treatment in the subgroup of the experimental population for which the questionnaire is validated (5-to-18 years of age).

5. SELECTION AND ENROLLMENT OF SUBJECTS

The study population includes 388 iron chelator naïve and not naïve patients affected by hereditary haemoglobinopathies (including but not limited to thalassaemia syndromes and SCD) and requiring chronic transfusion and chelation therapy.

Patients of both genders aged from 1 month to less than 18 years will be recruited. At least 10% of the patients will be from 1 month to less than 6 years of age.

Patients meeting inclusion/exclusion criteria as outlined in **Section 5.1** and in **Section 5.2** will be enrolled.

5.1Inclusion criteria

Patients will be eligible for inclusion in this study if the following criteria apply:

- patients of both genders aged from 1 month up to less than 18 years at the time of enrolment
- patients affected by any hereditary haemoglobinopathy requiring chronic transfusion therapy and chelation, including but not limited to thalassemia syndromes and sickle cell disease
- patients
  - on current treatment with DFO or DFX or DFP in a chronic transfusion program receiving at least 150 mL/kg/year of packed red blood cells (corresponding approximately to 12 transfusions)
  - naïve to chelation treatment who have received at least 150 mL/kg of packed red blood cells (corresponding to approximately 12 transfusions) in a chronic transfusion program and with serum ferritin levels ≥ 800 ng/mL at screening
- Until availability of results from the PK Study (Study DEEP-1, EudraCT n. 2012-000658-67) for patients aged from 1 month to less than 6 years: known intolerance or contraindication to DFO
- written informed consent obtained from patient’s legal guardian in accordance with the national legislations. Patient's informed assent will be collected according to his/her maturity and understanding.

5.2Exclusion criteria

A patient will not be eligible for inclusion in this study if any of the following criteria apply:

- patients with known intolerance or contraindication to either DFP or DFX
- patients receiving DFX at a dose > 40 mg/kg/day or DFP at a dose > 100 mg/kg/day at screening
- platelet count <100.000/mm^3 at the wash-out visit (day -7)
- absolute neutrophil count <1.500/mm^3 at the wash-out visit (day -7)
- Hb levels lower than 8g/dL at the wash-out visit (day -7)
- Evidence of abnormal liver function (ALT level >5xULN) at screening
- iron overload from causes other than trasfusional haemosiderosis
- severe heart dysfunction secondary to iron overload defined as the occurrence of heart failure or severe arrhythmia or cardiac MRI T2* lower than 10 ms available
- serum creatinine level > ULN for age at the wash-out visit (day -7)
- history of significant medical or psychiatric disorder
- the patient has received another investigational drug within 30 days prior to consent to study participation
- fever and other signs/symptoms of infection at the wash-out visit (day -7)
- concomitant use of trivalent cation-dependent medicinal products such as aluminium-based antacids
- positive test for β-HCG or lactating female patients.

5.3Study Enrolment Procedures

Patients meeting the inclusion/exclusion criteria will be randomized on Day 0 of the study, at a 1:1 ratio to one of the two groups of 194 patients (see **Section 6.6** for details on randomisation). One group will be treated with DFP, the other (control) group with DFX.

Informed consent will be requested to parents/legal guardians. Assent will be requested to children of a maturity sufficient to understand and capable of forming an opinion on the information provided, as stated in “Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to GCP in the conduct of clinical trials on medicinal products for human use” (2008, EudraLex Vol. 10 Chapter V). For further details, please refer to **Section 7.3.1**.

6. INVESTIGATIONAL MEDICINAL PRODUCTS

6.1 Deferiprone

Patients will be enrolled in the experimental arm at the DFP starting dose of 75 mg/kg/day or at their ongoing DFP dosage as long as this does not exceed 100 mg/kg/day.

In patients aged less than 6 years the initial dose will be defined according to the results of the PK study (Study DEEP-1). DFP should be taken daily 3 times-a-day: after breakfast, after lunch and after dinner, preferably at consistent times.

The investigational drug is provided as 80 mg/mL oral solution packaged in 250 mL amber polyethylene terephthalate bottles with threaded neck. White polypropylene child-resistant caps with foam liners have been used as closures.

An administration device that facilitates accurate measurement of appropriate dose volumes is provided. Since the formulation is intended for the entire paediatric group, two distinct administration devices (CE marked) will be provided: a graduated syringe (10 mL in steps of 0.2 mL) and a graduated measuring cup (30 mL in steps of 2.5 mL).

The patient, or the legal guardian of the patient, will be explained how to compose the patient's personal daily dose.

The total daily dose of DFP and the exact volume of solution per day will be calculated by the investigator based on the patient's body weight through the following formula:

$$\textbf{Total daily volume}\ (\text{mL}) = \frac{\text{dose level (mg/kg/day)} \times \text{body weight (kg)}}{80\ \text{mg/ml}}$$

Each administered dose is the total daily volume divided by three.

Every month, during the regular visits, the investigator will hand out an appropriate number of drug bottles to the patient and/or the legal guardian. Each bottle dispensed will be unambiguously characterized by the investigator through entering subject identifier and visit # on the provided space on drug label. The exact volume, the bottle identifier and the date of dispensation will be recorded in the Case Report Form (CRF). Medication returned by the patient will be counted and unused volumes will be tracked as well.

6.2Deferasirox

Patients will be enrolled in the control arm at a DFX starting dose which depends on patient current therapy at screening as summarised in **Table 3**.

Table 3. Starting dose for DFX arm

None (Naïve patient)	20 mg/kg body weight
Deferiprone	20 mg/kg body weight
Deferoxamine	Half DFO dose (but not less than 20 mg/kg body weight)
Deferasirox	Current patient's posology (but not higher than 40 mg/kg)

For all naïve patients and patients on DFP at screening the starting DFX dose will be 20 mg/kg body weight. If the patient's chelation therapy at screening is DFO, the starting dose of DFX will be numerically half that of the DFO dose (e.g. a patient receiving 40 mg/kg/day of DFO for 5 days per week (or equivalent) could be transferred to a starting dose of 20 mg/kg/day of DFX) but, in any case, to a starting dose not inferior to 20 mg/kg/day.

If the patient's chelation therapy at screening is DFX, the patient starting dose of DFX will be his/her current posology as long as this does not exceed 40 mg/kg.

An initial dose of 30 mg/kg will be allowed for patients who require reduction of elevated body iron levels (defined as serum ferritin level > 2500 ng/ml or MRI T2* < 20 ms).

DFX tablets will be available at dosage strengths of 125 mg, 250 mg and 500 mg DFX, in re-labelled commercial packs containing dispersible tablets in PVC/PE/PVDC/Aluminium blisters.

The individual daily doses of DFX and the tablets composition contributing to the daily dose will be calculated by the investigator based on the patient's body weight through the following formula:

Total daily dose (mg) = dose level (mg/kg/day) × body weight (kg)

Doses must be rounded to the nearest whole tablet size as recommended in the Exjade® SmPC (**Annex 1**).

DFX must be taken once a day on an empty stomach at least 30 minutes before food, preferably at the same time each day. The tablets can be dispersed by stirring in a glass of water or orange or apple juice (100 to 200 mL) until a fine suspension is obtained. Dispersion in carbonated drinks or milk is not recommended.

After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole.

6.3 Dose Adjustments

Dose adjustments for both DFP and DFX will be allowed for efficacy reasons (scaling up) or for safety reasons including the presence of markers indicative of over-chelation (scaling down).

DFP can be scaled up in steps of 12.5 mg/kg/day (to a maximum daily dose of 100 mg/kg) according to the individual patient's response defined as an increase of serum ferritin levels > 20% compared to the previous determination.

DFX will be scaled up in steps of 5 to 10 mg/kg (to a maximum daily dose of 40 mg/kg) according to the individual patient's response defined as an increase of ferritin levels > 20% compared to the previous determination.

For patients with a stable serum ferritin value >1500 (no increase or any increase <20%) and not showing a downtrend over a 3-month-period , DFP or DFX can be also increased.

DFP and DFX must be scaled down for the safety reasons detailed in **Table 4.**

Table 4. Scale down adjustment for DFP and DFX (safety reasons)

Serum creatinine increased by >33% from baseline or Reduction in creatinine clearance **(estimated with the Schwartz formula)** ≤ 90ml/min and >60 ml/min in two consecutive measurements	No dose adjustment.	Reduce DFX in steps of 10 mg/kg/day until value returns to baseline value and continue DFX with the adjusted dose for 1 month. If the increase persists interrupt DFX. If after DFX interruption value returns to baseline value or > 90 ml/min for creatinine clearance restart DFX at 50% of the last dose and then escalate by 10 mg/kg/day at 1 month intervals provided that value increase does not recur. Monitor serum creatinine, creatinine clearance and urine protein/creatinine ratio weekly (+/- 7 days) during the period of abnormal value and during the first month after dose modification, then monthly.
Urine protein/creatinine ratio ≥ 0.5 in two consecutive measurements	No dose adjustment.	Reduce DFX in steps of 10 mg/kg/day until value returns to < 0.5. If the increase persists interrupt DFX. After the ratio improves, restart DFX at 50% of the last dose and then escalate by 10 mg/kg/day at 1 month intervals provided that value increase does not recur. Monitor serum creatinine, creatinine clearance and urine protein/creatinine ratio weekly (+/- 7 days) during the period of abnormal value and during the first month after dose modification, then monthly.
ALT or AST > 10 ULN	Interrupt DFP. When levels return to < 5 ULN, restart DFP at 50% of the last dose and after 1 month scale it back up to the former dose.	Interrupt DFX. When levels return to < 5 ULN, restart DFX at 50% of the last dose and then escalate by 10 mg/kg/day at 1 month intervals provided that value increase does not recur.

Severe skin rash	No dose adjustment.	Interrupt DFX . Once resolved, restart DFX at 50% of the last dose and then escalate by 5 mg/kg/day at two-weeks intervals.
Ferritin ≤ 500 ng/ml	Reduce DFP to 50% of last dose. If ferritin is still <500 ng/ml at subsequent monthly evaluation, DFP may continue having consulted the Coordinating Investigator. When value returns > 500 ng/ml DFP can be scaled up to full dose.	Reduce DFX to 50% of last dose. If ferritin is still <500 ng/ml at subsequent monthly evaluation, DFX may continue having consulted the Coordinating Investigator. When value returns > 500 ng/ml restart DFX at 50% of the last dose and then escalate by 10 mg/kg/day at 1 month intervals.
Neutropenia(neutrophil count <1500/mm^3 and ≥1000/mm^3 in two consecutive measurements)*	Interrupt DFP and monitor neutrophil count every 1-3 days or more frequently. When value returns > 1500/mm3 for two consecutive measurements, and if deemed safe by the investigator, restart DFP at the last dose after having consulted the Coordinating Investigator.	Interrupt DFX and monitor neutrophil count every 1-3 days or more frequently. When value returns > 1500/mm^3 for two consecutive measurements, and if deemed safe by the investigator, restart DFX at the last dose after having consulted the Coordinating Investigator.
Moderate Neutropenia (neutrophil count <1000/mm^3 and > 500/mm^3) OR Severe Neutropenia/Agranulocytosis (neutrophil count < 500/mm^3)	Interrupt DFP. Exit from the protocol.	Interrupt DFX. Exit from the protocol.
Infection	Interrupt DFP until neutrophil count is checked. If neutrophil count is > 1500/mm^3, two consecutive measurements, and if deemed safe by the investigator, restart DFP at the last dose after having consulted the Coordinating Investigator.	Interrupt DFX until neutrophil count is checked. If neutrophil count is > 1500/mm^3, two consecutive measurements, and if deemed safe by the investigator, restart DFX at the last dose after having consulted the Coordinating Investigator.
Arthralgia	If symptoms persist after appropriate treatment, reduce DFP to 50% of last dose until resolution and then scale it back up to the former dose.	If symptoms persist after appropriate treatment, reduce DFX by 50% until resolution and then escalate by 10 mg/kg/day at 1 month intervals to the former dose.
Nausea/ Abdominal Pain/	If symptoms persist after appropriate treatment, reduce	If symptoms persist after appropriate treatment, reduce DFX

Vomiting	DFP to 50 mg/kg/day until resolution and then scale it back up to the former dose.	until resolution and then scale it back up to the former dose.

**** For details on clinical management of all neutropenia, please refer to Section 7.3.18 "Neutrophil count and Neutropenia management" and Section 16.6 "Instructions for rapid notification of Neutropenia".***

6.4Handling of investigational medicinal products

DFP will be supplied to the principal investigators by the Sponsor. A separate document will rule the agreement between the Sponsor and the MAH.

DFX will be supplied by each Centre as current therapy in compliance with the applicable national laws in the commercially available package and the label will be integrated in accordance with GMP requirements for the purposes of this study..

In any case, the Sponsor retains the responsibility of ensuring regular supply of both Investigational Medicinal Products (IMP) as ruled by GCP.

Medication labels of both IMPs will comply with the legal requirements of the countries where the study is implemented and be printed in the local language. They will supply no information about the patient. Only the subject identifier will be entered on the medication label under the investigator responsibility before the corresponding medication is handed out to the patient. The storage conditions and the consumption (in-use) period for study drug will be described on the medication label.

Both the experimental and the control medication used in this trial must be kept in an appropriate, secure area (e.g. locked cabinet) and stored according to the conditions specified on the drug labels. The investigator/competent pharmacist must maintain an accurate record of the storage temperature, of the shipment and dispensing of study drugs in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drugs dispensed to each subject must be kept by the investigator and made available for inspection at any time.
All drug supplies are to be used only for this protocol and not for any other purposes. Any partly-used or unused drug during the course of the study will be handled according to an *ad hoc* SOP. Destruction of unused/unusable investigational medicinal products and their empty containers should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted.
At the conclusion of the study, and, as appropriate during the course of the study, the investigator will follow the Sponsor's indications concerning the local disposal of any surplus and/or rejected materials. Unused/unusable investigational medicinal products and of all the empty drug containers should therefore not be destroyed without prior written authorisation by the Sponsor according to the conditions specified on an ad hoc SOP.

6.5Blinding

Blinding is not foreseen for this trial because of the different pharmaceutical forms and posology of IMPs which would have heavily impacted on the study feasibility.

6.6Randomisation

Patients will be stratified before randomisation into two groups according to age (<10 years and ≥10 years) considering their different capabilities in undergoing cardiac MRI T2*.

After stratification patients will be randomised on Day 0 of the study at the 1:1 ratio to one of two treatment groups. One group will be treated with DFP, the other (control) group with DFX.

Patients will be assigned a sequential patient number in each center at screening. Each patient will be unambiguously identified by a 6-digit subject identifier consisting of a 2-digit centre number and the 4-digit, sequential patient number. This subject identifier is unique and will not be changed throughout the entire study. Subject identification numbers of patients that did not meet the entrance criteria and were not randomised will not be re-used.

Randomisation will be determined centrally and balanced by country. The randomisation list will be printed out in advance at the start of the study. Since the number of recruited patients *per* centre cannot be determined *a priori*, a larger number of randomised numbers *per* country will be generated to allow a greater than anticipated number to be studied in the event that the enrolment rate in some specific centre is below expectations.

The randomisation number and the assigned treatment will be recorded in the source documents as well as in the CRF of the corresponding patient.

No fixed number of patients per age group will be specified upfront. However at least 10% of the patients recruited into the study will be aged from 1 month to less than 6 years.

7. CLINICAL AND LABORATORY EVALUATIONS

7.1Study outline

This study includes: a run-in period (maximum 28 days), a 12 months treatment period and a follow-up visit 1 month after last administration, as detailed below in **Figure 1**.

Figure 1: Study outline

The study procedures and outline develop as follows:

- Run-in period (day –28 to –1) divided in:
    - *Screening period* (day -28 to –7): Patients on their standard chelator schedule will be screened for eligibility. Two visits are foreseen in this period, the first one (Visit 1, between day -28 and day -8) to describe the study to the patient and to his/her parents and to obtain the informed consent, the second one (Visit 2, day -7) to assess the inclusion/exclusion criteria (see **Section 5.1** and Section **5.2**)

- *Washout period* (day –6 to –1): At day –6 patients will discontinue their ongoing chelator to start the washout phase.

The recruitment will start with the first eligible patient having signed informed consent and will continue for 12 months or less if the required number of patients has been reached.

- Treatment and observation period (month 1-month 12): the treatment period will start on Day 0 during V3 with randomization and will continue for 12 months. Patients will be visited every month. At each visit, assessments as detailed in **Table 5** will be conducted with a constant attention to the minimisation of pain and distress to the patient.

  Ferritin levels for efficacy assessments will be evaluated quarterly (centrally). Additionally, ferritin levels for patient's medical management will be evaluated monthly (locally).

  Cardiac MRI T2* in patients above 10 years of age able to undergo the MRI evaluation without sedation (regardless of their assignment treatment) will be assessed at baseline (V3), at month 6 (V9) and at the end of treatment (month 12, V15).

  Liver MRI will be assessed in all patients able to undergo the MRI evaluation without sedation (regardless of their assigned treatment) at baseline (V3) and at the end of treatment (month 12, V15).

Patients will continue with their regular transfusional regimen.

7.2Visit schedule and assessments

The schedule of all study evaluations is outlined in **Table 5**.

Table 5. Visit schedule and evaluations

	Run in			**Treatment**													
	Day			**Baseline** Day 0	Month												
	Screening -28→-8	-7	**washout** -6→-1		1	2	3	4	5	6	7	8	9	10	11	12	13 **Follow-up**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Demographic characteristics	X																
Randomization				**X**													
Informed consent	**X**																
Inclusion/exclusion criteria		**X**[1]															
Pregnancy test	**X**															**X**	
Physical examination	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Medical history and current medical conditions	**X**																
Pharmacokinetics[2]																**X**	
Vital signs	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Liver function history	**X**																
Heart function history	**X**																
Liver MRI[3]				**X**												**X**	
Serum Ferritin	**X**[9]			**X**	**X**[9]	**X**[9]	**X**	**X**[9]	**X**[9]	**X**	**X**[9]	**X**[9]	**X**	**X**[9]	**X**[9]	**X**	**X**[10]
ECG	**X**			**X**			**X**			**X**			**X**			**X**	
Cardiac MRI T2*[4]				**X**						**X**						**X**	
Urinalysis	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Renal function[5]	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Haemoglobin	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Neutrophil count[6]	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hepatitis serology	**X**															**X**	
Haematology/ Biochemistry[7]	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**[10]

Ocular and audiometric test[8]				**X**												**X**	
Concomitant medications				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Medical events				**X**													
Adverse events					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Body height/weight	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pubertal staging				**X**						**X**						**X**	
Compliance					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
CHQ questionnaire				**X**						**X**						**X**	**X**[10]
Healthcare Resouces					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

[1]*Results of platelet count, neutrophil count, haemoglobin and serum creatinine must refer to blood test performed on day -9 to day -7. Serum creatinine must be assessed in duplicate (for the assessment of inclusion/exclusion criteria only)*

[2]*Treatment drug should be administered in the clinic under supervision of qualified staff and time recorded accordingly. A sample (2 mL) for the assessment of peak drug concentrations should be collected within 4 hours after dosing according to the sparse sampling scheme specified in the SPM*

[3]*Liver MRI is allowed to be performed ±20 days from the scheduled date*

[4]*Cardiac T2*MRI is allowed to be performed ±20 days from the scheduled date*

[5]*Serum creatinine and serum creatinine clearance(calculated through Schwartz formula) will be performed weekly* (± 7 days from the scheduled date) *for the first month of treatment and monthly thereafter*

[6]*Neutrophil counts must be performed weekly (±7 days from the scheduled date) from the start of treatment*

[7]*Serum transaminases, bilirubin and alkaline phosphatase will be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter*

[8]*Ocular and audiometric examination are allowed to be performed ±20 days from the scheduled date*

[9] *Ferritin at V1, V4, V5, V7, V8, V10, V11, V13 and V14 will be evaluated only at the local laboratory. All other ferritin assessments will be evaluated at both the local and central laboratory/ies.*

[10]*Central ferritin, haematology/biochemistry and CHQ will be evaluated also in case of withdrawal (withdrawal visit).*

The clinical assessments will be conducted at each scheduled visit. The timing of each visit is listed in **Table 5.** Each visit will be scheduled at the same day of the month ± 7 days. MRI evaluations (cardiac and hepatic) will be allowed ± 20 days deviation from the scheduled visit.

Further information is provided in the following sections and detailed procedures for conducting each assessment are provided in the Study Procedures Manual (SPM).

At each visit, following completion of all procedures, the patient will be discharged from the unit.

7.2.1 Pre-randomisation evaluations

These evaluations occur prior to the patient receiving any study intervention.

Run-in – Screening period: **V1** (day -28→-8)
A signed Informed Consent Form and, when applicable, an Assent Form will be obtained before any other study-specific assessments are performed.
Informed Consent Form and Assent Form will be collected at V1, being this visit performed between day -28 and day -8.
Between day -28 and day -8 the following screening assessments will be performed and collected:

- Demographic characteristics
- Pregnancy test
- Clinical physical examination
- Medical history and current medical conditions
- Vital signs
- Liver function history
- Heart function history
- Serum Ferritin
- ECG
- Urinalysis
- Renal function
- Hepatitis serology
- Haematology/Biochemistry
- Body height/weight

Platelet count, neutrophil count, haemoglobin and serum creatinine must be assessed between day -9 and day -8 or, alternatively, at day -7 at the wash-out visit (V2).

Additional information regarding clinical procedures will be provided in the SPM.

Run-in – Screening period: Wash-out visit **V2** (day -7)
V2 will be performed at day -7. This visit is meant to assess the patient for inclusion/exclusion criteria on the basis of the examinations/evaluations performed during the screening period. Platelet count, neutrophil count, haemoglobin and serum creatinine, if not assessed at day -9 or day -8 of the screening period, must be evaluated at the time of this visit (V2, day -7).

During this visit patients will be also required to suspend any ongoing chelation treatment from day -6 to day -1.

Additional information regarding clinical procedures will be provided in the SPM.

Run-in: Wash-out period (day -6→-1)

Patients are required to suspend any ongoing chelation treatment from 00.00 hrs of day -6 to day -1. Chelation naïve patients will not respect the same time period before starting treatment and the wash-out phase is not foreseen. No visits are foreseen in this period.

Baseline (Study Entry): **V3** (Day 0)

This visit will be completed 6 days after any ongoing chelation treatment has been withdrawn (wash-out).

The study intervention (DFP or DFX) will be assigned to the patients according to randomisation.

The following assessments will be performed before trial treatment administration:

- Randomisation
- Clinical physical examination
- Vital signs
- Liver MRI
- Serum Ferritin
- ECG
- Cardiac MRI T2*
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Haematology/Biochemistry
- Concomitant medications
- Medical events (as events occurred after the signature of the Informed consent)
- Body height/weight
- Ocular examination
- Audiometric examination
- Pubertal staging (according to Tanner, see **Section 10.1**)
- CHQ

Liver MRI and cardiac MRI T2* are allowed to be executed at day 0 ± 20 days.

At the completion of the evaluation, the patient will be randomised to one of the two study treatments and is provided with the assigned intervention (sufficient for one-month treatment) and instructions for dose preparation and administration. DFP and DFX treatments must start at day 0.

Additional information regarding clinical procedures will be provided in the SPM.

7.2.2 On-Study/On-Intervention evaluations

V4/month 1, **V5**/month 2, **V7**/month 4, **V8**/month 5, **V10**/month 7, **V11**/month 8, **V13**/month 10, **V14**/month 11 assessments

These visits will be completed on the same calendar day (±7 days) of the appropriate month as the baseline evaluation.

At each visit the following assessments will be performed:

- Clinical physical examination
- Vital signs
- Serum ferritin
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Haematology/Biochemistry
- Concomitant medications
- Adverse events
- Body height/weight
- Compliance
- Healthcare resources

Additional information regarding clinical procedures will be provided in the SPM.

V6/month 3 assessments

These visits will be completed within the same calendar day of the month (±7 days).

At each visit the following assessments will be performed:

- Clinical physical examination
- Vital signs
- Serum Ferritin
- ECG
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Haematology/Biochemistry
- Concomitant medications
- Adverse events
- Body height/weight
- Compliance
- Healthcare resources

Additional information regarding clinical procedures will be provided in the SPM.

V9/month 6 assessment

This visit will be completed within the same calendar day of the month (±7 days).

The following assessments will be performed:

- Clinical physical examination

- Vital signs
- Serum Ferritin
- ECG
- Cardiac MRI T2*
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Haematology/Biochemistry
- Concomitant medications
- Adverse events
- Body height/weight
- Pubertal staging (according to Tanner, see **Section 10.1**)
- Compliance
- CHQ
- Healthcare resources

Additional information regarding clinical procedures will be provided in the SPM.

V12/month 9 assessments

These visits will be completed within the same calendar day of the month (±7 days).

At this visit the following assessments will be performed:

- Clinical physical examination
- Vital signs
- Serum Ferritin
- ECG
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Haematology/Biochemistry
- Concomitant medications
- Adverse events
- Body height/weight
- Compliance
- Healthcare resources

Additional information regarding clinical procedures will be provided in the SPM.

7.2.3 On-Study/Off-Intervention evaluations

This visit will occur only if the patient withdraws consent or the investigator identifies medical reasons to withdraw the patient from the study. In this event, all the assessments included in the V16/ follow up assessments will be conducted.

7.2.4 Final On-Study evaluations

V15/month 12 assessment

This visit will be completed within the same calendar day of the month (±7 days) and constitutes the final on treatment evaluation.

The following assessments will be performed:

- Pregnancy test
- Clinical physical examination
- Pharmacokinetics
- Vital signs
- Liver MRI
- Serum Ferritin
- ECG
- Cardiac MRI T2*
- Urinalysis
- Renal function
- Haemoglobin
- Neutrophil count
- Hepatitis serology
- Haematology/Biochemistry
- Concomitant medications
- Adverse events
- Body height/weight
- Ocular examination
- Audiometric examination
- Pubertal staging (according to Tanner, see **Section 10.1**)
- Compliance
- CHQ
- Healthcare resources

On this visit day, the treatment drug should be administered in the clinic under supervision of qualified staff and time recorded accordingly. Accurate assessment of the pharmacokinetics of DPF and DFX will require that blood sampling and time of last dose administration will be recorded.

Additional information regarding clinical procedures will be provided in the SPM.

7.2.5 Off-Study requirements

V16/month 13 follow up assessment or withdrawal visit

This visit should be completed one month (± 7 days) after Visit 15 or in case of withdrawal. The following assessments will be performed:

- Clinical physical examination
- Vital signs
- Concomitant medications
- Adverse events
- Body height/weight

In case of withdrawal, centralized serum ferritin and CHQ will be also assessed.

Additional information regarding clinical procedures will be provided in the SPM.

7.3 Special instructions and definitions of assessments

7.3.1 Randomisation

Randomisation will occur at Day 0 of the study. Patients will be randomised at a 1:1 ratio to one of the two treatment group DFP or DFX. The randomisation list will be determined centrally before the study start.

Other details about randomisation are provided in **Section 6.6.**

7.3.2 Informed Consent

As subjects enrolled in this study are below the legal age and cannot consent for themselves, signed Informed Consent Form will be obtained from both parents, legal guardian, or person with power of attorney. Additionally, the subject's assent will also be obtained if he or she is able to understand the nature, significance, and risks associated with the study.

As recommended by the European framework (Directive 2001/20/EC; Additional protocol on biomedical research, 2005; Ethical Recommendations, 2008), full comprehensive information will be given from the primary caregiver to all the legal representatives as well as the potentially eligible children for the trial before the written full informed consent.

Written and oral information will be given in language and wording appropriate to age, psychological and intellectual maturity and taking into account the cultural and linguistic differences. Information will be presented clearly, using short sentences and either avoiding or explaining all technical terms. They have to deal with:

- the rationale and objectives of the study;
- possible risks and potential and direct benefits associated with trial treatment;
- the arrangements for responding to AEs or the concerns of research participants;
- the nature, extent and duration of the procedures and, especially, the details of the extra burden caused by the trail;
- insurance information and the arrangements for fair compensation in the case of damage;
- the arrangements to ensure respect for private life and confidentiality of the individual data arising from the research;
- the arrangements for accessing information produced by the study and relevant to the participant;
- the rights and safeguard dictated by law for the child protection;

- the right to freely refuse or to withdraw from the trial at any time for any reason without any disadvantage or prejudice without reasoning the decision and without being subject to any liability and/or to any form of discrimination, in particular regarding his/her right to medical care.

Separate information sheets describing the study's objectives and procedures, elaborated in a form which will take into account the cultural and linguistic differences in the study population, will be provided to the parent/legal guardian prior to the submission of the Informed Consent Form. The parent/legal guardian will be provided an Informed Consent Form in his/her National language to be signed only upon agreement of the terms and conditions included in the document.

All the time necessary to freely decide the involvement of a subject in the clinical trial will be made available.

In addition, and in accordance with the "Ethical Considerations for Clinical Trials Performed in Children", Recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to GCP in the conduct of clinical trials on medicinal products for human use, separate information sheets specifically elaborated for children and adolescents, in language and wording appropriate to age, psychological and intellectual maturity, and taking into account the cultural and linguistic differences, will be provided to each patients in order to inform him/her on the study's objectives and procedures and obtain his/her assent to the participation to the study.

According to the European Ethical Recommendations (2008), if the child's assent is not obtained, this should be documented in the Informed Consent Form which is signed by the parent/legal representative and investigator.

The Informed Consent Form must be signed and personally dated by the legal representative and the Investigator / Co-Investigator. The original copy of the signed forms will be retained with the source documents in the trial site and a copy will be given to the family/participant.

Upon parents' and/or participant's consent, a letter will be sent to the participant's primary care doctor informing him/her of the involvement of his/her young patient in the trial, the treatment, the concomitant other medicinal products not permitted.

Carers and participants are free to refuse to participate to the trial or withdraw their consent at any time and for every reason.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient.

7.3.3 Inclusion/exclusion criteria

During the screening period (day-28 to day -7), the patient will execute examinations/evaluations allowing the assessment of inclusion/exclusion criteria set in **Section 5.1** and **Section 5.2**. Inclusion/exclusion criteria must be satisfied at the time of the washout visit (V2, day -7) before starting the wash-out period.

7.3.4 Pregnancy test

For females with childbearing potential a pregnancy test (β-HCG) will be carried out locally on serum during the screening period (V1) and at the end of treatment (V15). During the treatment of the study pregnancy testing (β-HCG) will be repeated if pregnancy is suspected.

Fertile and sexually active male or female patients should be advised to use an approved method of contraception from time of enrolment (V1), throughout the course of the trial, and for 30 days following early termination or the last visit (V16).
In the situation where a female patient becomes pregnant, study medication must be stopped immediately and the patient is withdrawn from the study, and procedures outlined in **Section 16.5** must be followed.

Male patients must inform the Investigator if their female partner becomes pregnant during the trial or within one month after trial completion. Procedures outlined in **Section 16.5** must be followed. However, there will be no requirement for the male patient to be withdrawn from the trial.

The Investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy, and the outcome should be transmitted to the Sponsor as well.

Approved methods of contraception will consist of the following for the purposes of this study or must follow local requirements:

• Oral contraceptive medications with condom or spermicide

• Hormonal implants with condom or spermicide

• Injectable contraceptive medications with condom or spermicide

• Condom used with spermicide.

If the hormonal contraception is used, it should have a Pearl index <1%.

[All statements in this section should apply without prejudice and fully respecting the ethical and religious habit of the concerned patient.]

7.3.5 Clinical physical examination

Clinical physical examination will be performed at each visit (V1 to V15) and at V16 (follow-up).

7.3.6 Medical history and current medical conditions

Anamnesis and medical history will be assessed at screening (V1). Significant findings must be included in the CRF. Current medical conditions will be also recorded at screening (V1) as part of the patient medical history.

7.3.7 Pharmacokinetics

Pharmacokinetic assessment will be performed in patients who complete the study. Last dose of the study treatments (DFP and DFX) must be administered in the clinic under supervision of qualified staff at the beginning of the visit V15 and time of administration must be recorded accordingly and reported in the CRF. A sample (2 mL) for the assessment of peak drug concentrations should be collected within 4 hours after dosing according to the sparse sampling scheme specified in the SPM.

7.3.8 Vital signs

Blood pressure and pulse rate will be assessed during screening (V1), at baseline (V3) and monthly thereafter at scheduled visits (V4 to V16) during the treatment and observation period. Systolic and diastolic blood pressure and pulse rate will be measured after the subject has rested in the sitting position for at least 3 minutes. Blood pressure should be assessed at the same arm each time.

7.3.9 Liver function history

For the comprehensive documentation of the patient's liver condition the following data will be collected at screening (V1): history of hepatitis, cirrhosis, results from liver biopsy, if available.

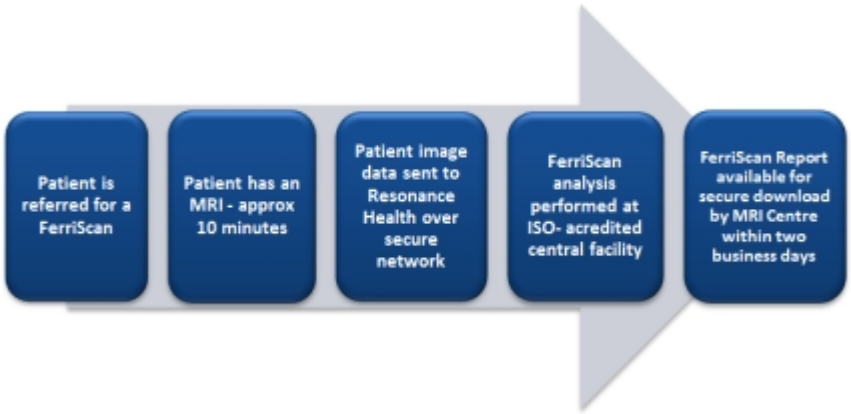
7.3.10 Heart function history

For the comprehensive documentation of the patient's heart condition any record documenting severe heart dysfunction and arrhythmia will be collected at screening (V1).

7.3.11 Liver MRI

Liver MRI will be assessed in all patients able to undergo the MRI evaluation without sedation (regardless of their treatment assignment) at day 0 (V3)±20 days and month 12 (V15)±20 days, adopting the MRI-based FerriScan® technology from Resonance Health Ltd.
Patients will be referred to an MRI Centre for a FerriScan evaluation by the investigator. The scan data acquired will be sent to the Resonance Health central processing facility by secure transmission. A quality controlled analysis process will provide a LIC report available for download by the MRI centre.
MRI instrument specifications: the process uses patented spin density projection R2-MRI imaging technology. Each MRI screening centre will be equipped with a MRI scanner with a field strength of 1.5 Tesla.
MRI instrument calibration verification: FerriScan will be provided as a service to MRI Centres selected after assessing the suitability of their scanners for the protocol.
A Service Agreement will be established with the MRI Centres, and an Instruction Manual will be provided on all aspects of the FerriScan analysis service. A Phantom Pack will be provided by Resonance Health Ltd to complete the validation and set-up process in the MRI centres. Scan data will be transmitted for analysis at the Resonance Health quality-controlled central processing facility. Once the Phantom Pack will be successfully scanned, the MRI Centre will receive confirmation that patient scanning may commence.
Data Analysis: MRI images will be captured and securely transmitted to the Resonance Health ISO9000 and ISO13485 accredited analysis facility. The patented FerriScan analysis procedure will produce a map of liver iron and will calculate a mean LIC measurement. Results will then be available for secure download within a target time of 48 hours.
Scan data will be transmitted to the Resonance Health service centre through a secure web-based portal. Only authorised persons from MRI facilities will then be able to track its progress through the FerriScan Analysis Service Tracking system (FAST).
A LIC report will be available for download within two working days.
Evaluation procedure: the MRI evaluation process is outlined in **Figure 2**.

Figure 2. MRI evaluation procedure.



7.3.12 Serum Ferritin

All the determinations relative to serum ferritin will be carried out on the same sample collection as haematology/biochemistry at screening, and at each monthly visits for evaluation at the local laboratory for patient clinical monitoring.
Additional serum ferritin determinations will be performed in blood collected in separate vials at V3, V6, V9, V12, V15 and will be evaluated in the centralised laboratory/ies as specified in the SPM. Central determination of ferritin will be performed also in case of withdrawal during the early termination visit. Central determinations will be used for formal analyses.

7.3.13 ECG

A standard 12-lead electrocardiogram (ECG) will be performed during screening (V1), at baseline (V3) and every 3 months during the treatment and observation period at scheduled visits (V6, V9, V12, V15). The same physician at the centre will interpret all ECGs to maintain consistency. The tracings will be measured, interpreted, dated, signed and must be filed in the hospital record. ECG tracings must show at least 5 R-R intervals, in order to allow proper calculations of the QT corrected times. The subject's number and initials, the date and actual time of the tracing, and "Study DEEP-2" must appear on each page of the tracing.

7.3.14 Cardiac MRI T2*

Cardiac MRI T2* will be assessed in patients above 10 years of age able to undergo the MRI evaluation without sedation (regardless of their treatment assignment) at day 0 (V3)±20 days , at month 6 (V9) ±20 days and at month 12 (V15) ±20 days.
The Cardiac T2* imaging protocol and the analysis are provided at Resonance Health's central image analysis facility under its quality controlled environment.
Patients will be referred to an MRI Centre to acquire cardiac T2* images. The scan data acquired will be sent to the Resonance Health central processing facility by secure transmission. A quality controlled analysis process will provide a result report available for download by the MRI centre.
MRI instrument specifications: the MRI scanner with field strength of 1.5 Tesla will be equipped with a cardiac MRI package that includes:

- RF coil suitable for acquiring cardiac images
- ECG facility
- Single breath-hold, multi-echo T2* sequence with:
  Total of 8 echo times

Minimum TE between 2 and 3 ms
Maximum TE between 16 and 23 ms

MRI instrument calibration verification: cardiac T2* image analysis will be provided as a service to MRI Centres selected after assessing the suitability of their scanner. Centres not equipped with a scanner or equipped with an unsuitable instrumentation will be referred to another equipped Centre.
A Service Agreement will be established with the MRI Centres, and an Instruction Manual will be provided on all aspects of the service.
Data Analysis: MRI images will be captured and securely transmitted to the Resonance Health ISO9000 and ISO13485 accredited analysis facility. Results will then be available for secure download within a target time of 48 hours.
Scan data will be transmitted to the service centre through a secure web-based portal. Only authorised persons from MRI facilities will then be able to track its progress through the system.
A cardiac MRI T2* report will be available for download within two working days
Evaluation procedure: the MRI evaluation process is outlined in Figure 2.

7.3.15 Urinalysis

Complete urinalysis and proteinuria assessed as urine protein/urine creatinine ratio on a fresh sample will be assessed at screening (V1), at baseline (V3) and monthly (V4 to V15) and weekly (± 7 days) during the first month after initiation or modification of therapy, as indicator of tubular and/or glomerular damage.

7.3.16 Renal function

Renal function will be assessed as serum creatinine and creatinine clearance calculated according to Schwartz formula. Both parameters will be determined at each scheduled study visit (V1 to V15) and weekly (± 7 days) during the first month after initiation or modification of therapy.
Serum creatinine for checking exclusion criteria must be assessed in duplicate between day -9 and day -7 of the screening period.

7.3.17 Haemoglobin

Haemoglobin level will be monitored at each scheduled study visit (V1 to V15). Haemoglobin level for checking exclusion criteria must be assessed between day -9 and day -7 of the screening period.

7.3.18 Neutrophil count and Neutropenia management

The measurement of absolute neutrophil counts will be done weekly (±7 days), possibly at each scheduled visit for an early identification of cases of neutropenia and agranulocytosis. In case of infection neutrophil count should be monitored more frequently. Neutrophil count for checking exclusion criteria must be assessed between day -9 and day -7 of the screening period.

Neutropenia is defined as any ANC < 1500/mm3 confirmed in two consecutive measurements. If both consecutive counts are below 1.5 x 10^9/L but are not within the same range, a third count is required to determine the severity category. Neutropenia is considered to be resolved when ANC is ≥1.5 x 10^9/L on 2 consecutive counts.

Mild Neutropenia* (ANC ≥1000/mm^3 and < 1500/mm^3 in two consecutive measurements)

Moderate Neutropenia* (ANC ≥ 500/mm^3 and < 1000/mm^3 in two consecutive measurements)

Severe Neutropenia/Agranulocytosis* (ANC <500/mm^3)

The handling and follow up of the patient will depend on the severity of the neutropenia (mild, moderate, severe/agranulocytosis) as follows.

Mild Neutropenia:

- treatment must be interrupted and patient's ANC must be monitored every 1-3 days, or more frequently, until resolution of the event, defined as two consecutive ANC ≥ 1500/mm^3.
- If the patient has a mild neutropenia and develops signs of infection (fever), therapy must be interrupted immediately and ANC must be obtained and monitored every 1-2 days, or more frequently, until resolution of the event.
- Provide protective isolation; treat the patient as per clinical need and per local protocol (antibiotic therapy, admission to hospital if clinically indicated). If possible, hemocolture, throat swab, viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine will be collected.
- Therapy with DFP or DFX and continuation of trial can be restarted once all symptoms have been resolved and when it is deemed safe by the Investigator, after having consulted the Coordinating Investigator, in accordance with Table 4, Section 6.3 "Dose Adjustment".

Moderate Neutropenia

- treatment must be interrupted and the patient must be withdrawn from the study and monitored until resolution of the event;
- provide protective isolation; if clinically indicated, admit patient to hospital, obtain regular vital signs and treat the patient as per clinical need and per local protocol (antibiotic therapy and/or granulocyte colony stimulating factor).
- the patient will be examined the same day, if possible, collecting drug history and physical examination;
- if possible, hemocolture, viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine will be collected.

Severe Neutropenia/Agranulocytos

- treatment must be interrupted immediately and the patient must be withdrawn from the study and monitored until resolution of the event;
- provide protective isolation; if clinically indicated, admit patient to hospital, obtain regular vital signs and administer appropriate therapy such as antibiotic therapy and granulocyte colony stimulating factor, beginning the same day that the event is identified;
- the patient will be examined the same day, if possible, collecting drug history and physical examination;
- if possible, hemocolture, viral studies (CMV, parvovirus, hepatitis A/B/C), serum ALT, BUN, creatinine will be collected.
- the patient will be monitored daily or more frequently until two successive ANCs are ≥ 1500/mm^3.

All neutropenia, irrespective of their severity or seriousness must follow the expedite reporting of SAE, as indicated in Section 16.6 "Instructions for rapid notification of Neutropenia".

7.3.19 Hepatitis serology

At screening (V1)and at visit V15 the following tests on hepatitis serology will be performed at the local laboratory:

- Hepatitis B screening to document the state of immunisation of past infection or active infection (HBsAg and HBsAb)
- Hepatitis C screening to document past or active infection with HCV RNA (quantitative)

All tests on hepatitis serology will be carried out on the same sample as collected for blood haematology/biochemistry.

7.3.20 Haematology/Biochemistry

All haematology/biochemistry will be performed in the local laboratory and will be assessed at each scheduled visit (V1 to V15 and at withdrawal visit when applicable) for the monitoring of transfusion requirements.
Complete blood count will be evaluated monthly.
Serum transaminases, bilirubin and alkaline phosphatase will be checked before the initiation of treatment, every 2 weeks during the first month and monthly thereafter.
Platelet count for checking exclusion criteria must be assessed between day -9 and day -7 of the screening period.

7.3.21 Ocular and audiometric test

Ocular examinations will be performed at baseline (V3 ±20 days) and at the end of treatment (V15 ±20 days).

An audiometric examination will be performed at V3 ±20 days and then at V15 ±20 days.

7.3.22 Pharmacokinetics

Samples collection for pharmacokinetics on V15 will consist of an additional 2ml blood each to allow for the assessment of steady state concentrations of DFP and DFX.
Whilst timing of dose and blood collection are not strictly defined throughout the study visits, patients are expected to take the last dose in the clinic, under supervision of qualified staff.
Blood sampling for pharmacokinetics (2 ml) for the assessment of peak drug concentrations should be collected within 4 hours after dosing according to the sparse sampling scheme specified in the SPM. It is critical that both sampling and dosing time are accurately recorded.

7.3.23 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event CRF and followed as appropriate.
For details please refer to **section 16**.

7.3.24 Body height/weight

Auxological parameters such as weight and height will be evaluated at each monthly visit at V1 and from V3 to V15.

7.3.25 Pubertal staging

Pubertal stage measured according to Tanner staging system will be assessed at V3, V9 and V15.

7.3.26 Compliance

Compliance will be assessed at each visit from V4 to V15 by estimating DFP solution volume in each bottle or the number of DFX tablets in the blister pack remaining at each visit.

7.3.27 Quality of Life

QoL questionnaire will be assessed to evaluate the Health Related Quality of Life (HRQoL) from the point of view of parents or guardians of patients aged from 5 to less than 18 years through CHQ. CHQ will be filled in at V3, in V9 and at the end of treatment (V15) and scoring will be reported in the CRF.

7.3.28 Healthcare Resources

Healthcare resources as reported in **Section 4.4.6** will be assessed at each monthly visit from V4 to V15 and the following parameters will be recorded in the CRF: hospitalisation (ward, length of hospitalisation), outpatient visits (type of visit), tests performed outside those foreseen in the protocol.

8. CONCOMITANT MEDICATIONS

Regular medications needed to treat concomitant medical conditions may be continued during the study. Such concomitant medications must be recorded in the CRF. Patients must be instructed not to take any additional medications (including over-the counter-products) during the study without prior consultation with the investigator except those accepted by the investigator at screening. If concomitant therapy must be added or changed, the reason and name of the drug should be recorded on the CRF.

Due to the unknown mechanism of DFP-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis. Drugs reported to be associated with agranulocytosis include antimicrobial agents (chloranphenicol, penicillins, sulphonamides), analgesic/anti-inflammatory agents (aminopyrine, indomethacine, phenylbutazone), anticonvulsivants (phenytoin, carbamazepine), anthithyroid agents (propylthiouracil), cardiovascular agents (hydralazine, procainamide, quinidine), hypoglycaemic agents (chlorpropamide), sedative (chlorpromazine, phenothiazines).

For any drug interaction concern with DFX, please refer to section 4.5 (Interaction with other medicinal products and other forms of interaction) of the DFX SmPC (Annex 1).

Potential drug interactions

Data indicate that DFP and DFX are primarily metabolised by UGT enzymes. Medications that are strong inhibitors or inducers of human UGT (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, ritonavir) will be prohibited during the study treatment.

Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name, dose administered and the dates of administration are to be recorded.

Prohibited Medications

Subjects must abstain from taking known drugs that interfere with chelation. Patients and/or their parents/legal guardians must be instructed to use aluminium-containing therapies only after consultation with the investigator.

Non-Drug Therapies

Subjects should abstain from taking any non-prescription medication, vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug (Day 0) until completion of the follow-up visit (V16, month 13), unless in the opinion of the Investigator and Sponsor the medication will not interfere with the study.

9. INTERRUPTION OF TREATMENT

This section deals with a patient's premature withdrawal from the study before completing all scheduled visits. An individual subject may be withdrawn at the discretion of the responsible investigator and the study team for the reasons listed hereby. In the event one or more subjects are withdrawn, additional subjects may be enrolled to ensure an adequate number of subjects complete the cohort.

Reasons that a patient must discontinue participation in a clinical study are considered to constitute one of the following:

1. unsatisfactory therapeutic effect (quarterly increase in ferritin levels of at least 1500 ng/ml as detected by two determinations performed at no more than two weeks interval, or if cardiac MRI T2* decreases under 10ms)
2. subject's condition no longer requires study treatment
3. DFX treatment at 10 mg/kg/day (for safety reasons) for more than 4 weeks
4. DFP or DFX administration suspended (for safety reasons) for more than 4 weeks
5. adverse event(s) requiring change of chelation therapy, including moderate or severe Neutropenia
6. significant protocol violation
7. subject/legal guardian withdrew consent/assent
8. lost to follow-up
9. administrative problems
10. death

In the absence of a medical contraindication or significant protocol violation, the investigator may make an effort to keep the subject in the study. Should a subject withdraw or be withdrawn by the legal guardian, he/she has to complete a full set of the 'end-of-study phase assessments', i.e. a full V16 evaluation. Relevant records will have to be done on the corresponding CRF pages.

This requirement does not refer to patients who passed the screening and washout period and were found not to be eligible for treatment.

Patients prematurely withdrawn from the treatment will be considered treatment failures.

10. SPECIAL METHODS AND SCALES

10.1 Pubertal staging

Tanner scale:

- Male and female patients

I Preadolescent, no sexual hair

II Sparse, pigmented, long, straight, mainly along labia and at base of penis
III Darker, coarser, curlier
IV Adult, but decrease distribution
V Adult in quantity and type with spread to medial thighs

- Female patients, breast

I Preadolescent
II Breast budding
III Continued enlargement
IV Areola and papilla form secondary mound
V Mature female breast

11. STATISTICAL CONSIDERATIONS

11.1 General Design Issues

This is a multicenter trial primarily aimed at demonstrating the non-inferiority of DFP to DFX in terms of percentage of successfully chelated patients after one-year treatment.

A non-inferiority study is considered the appropriate design for this trial for the reasons outlined in **Section 4** and further detailed below. No studies directly comparing DFP and DFX are available, however extensive literature is published comparing the efficacy of both IMPs with DFO. In particular, DFP results as efficacious as DFO in reducing serum ferritin levels in several studies in adults and children (Olivieri et al, 1990; Olivieri & Brittenham, 1998; Aydinok et al, 1999, 2007; Maggio et al, 2002; Maggio et al, 2010; Gomber et al, 2004; Galanello et al, 2006; Ha et al, 2006; Pennell et al, 2006; Cappellini MD et al. 2006; Tanner et al, 2008; El-Beshlawy et al, 2008). Concerning DFX, a recent Cochraine review showed that an efficacy comparable to DFO can be achieved depending on the ratio of doses of DFO and DFX being compared; similar or superior efficacy for ferritin and LIC could only be achieved in the highly iron-overloaded subgroup treated at mean doses between 28 and 52 mg/day (Meerpohl JJ et al, 2012).

The analysis is based on a success criterion defined in terms of serum ferritin and cardiac iron load (see **Section 4.3**) applied to paediatric population affected by hereditary haemoglobinopathies requiring chronic transfusion and chelation.

A composite outcome measure including ferritin and cardiac MRI T2* is considered an updated and multi-factorial clinical evaluation of iron overload in this experimental population, as further detailed in **Section 4.** As cardiac MRI T2* evaluation is generally uninformative and burdensome under 10 years of age because of the need of sedation, the outcome measure has been tailored to the age of the patient at a threshold of 10 years.

A successfully chelated patient in this trial is hence defined as follows:

- a patient satisfying the criterion A in **Section 4.3.1** based on ferritin levels if the patient is < 10 years of age;
- a patient satisfying criterion A and criterion B in **Section 4.3.1** based on both ferritin levels and cardiac MRI T2* in patients ≥ 10 years of age.

For ethical reasons, the sole criterion A will be applied also to patients ≥ 10 years of age who would require sedation during the MRI assessment.

The choice of this composite endpoint allows the feasibility of the trial in the entire paediatric population and provides an up to date approach to the evaluation of the global iron accumulation in paediatric transfusion-dependent patients. In addition the use of a composite endpoint (rather than an alternative one) allows avoiding multiplicity while adequately characterising (total body iron load and in the heart) the beneficial effect of treatments.

Each component of the composite endpoint will be considered for secondary analyses with the intent to clarify the interpretation of the composite. For such analyses no adjustment for multiplicity will be foreseen (see **Section 11.2**).

Based on the above defined composite endpoint, non inferiority is established if the lower limit of two sided 95% confidence interval of the difference in success rate is above - 12.5%. The choice of this margin is based on clinical considerations starting from the available evidences for the effects of DFP and DFX on ferritin levels and cardiac iron load.

In details, the percentage of expected success for DFX and DFP measured as change from baseline to 1 year treatment is summarised in the following **Table 6**:

Table 6: Success rates for DFP and DFX

Serum ferritin levels	76% (95%CI: 63.6-88.5) DFP mean dose 66.4 mg/kg/day *(Addis A et al, 1999)* *Paediatric population included in the meta-analysis but not analysed separately.*	57% (95%CI: 50.7-63.3) DFX used at 20-30 mg/kg/day *(Taher A et al, 2009*) *75 adult and 162 paediatric patients*
Cardiac MRI T2*	66% Higher percentage in splenectomised patients *(Pennell DJ et al, 2006)* *29 adults*	69.5% in patients with moderate-to-mild baseline cardiac iron load (≥10 to <20 ms) DFX mean dose 33.1±3.7 mg/kg/day *(Pennell DJ et al, 2010)* *72 adult and 29 paediatric patients*

Pooling together these findings, the expected percentage of success in the composite endpoint is assumed to be equal to 65% and 67.5% for DFX and DFP, respectively. The non inferiority margin of 12.5% has been considered to be a good estimate of an achievable lower bound of the true difference between the DFP and DFX.

Other secondary objectives include the evaluation of treatment efficacy in terms of liver iron concentration, the assessment of treatment safety and tolerability profiles, healthcare resources utilisation and patient global assessment and the analysis of the relationship of the demographic covariates and the disposition of DFP.

The correlation between DFP and DFX disposition and serum ferritin levels after 1 year treatment will be tested as exploratory objective of the trial.

11.2 Study population

Intent to treat population

For the intent to treat (ITT) analysis all patients that have been randomized and start therapy will be included.

Per protocol population

Patients in the per protocol (PP) population for the primary efficacy analysis (PP1) are those that have received the study drugs and for whom the composite endpoint is available at baseline and after 1 year treatment, without major protocol violations.

For the secondary efficacy evaluation assessed as non-inferiority of DFP to DFX in terms of serum ferritin levels the PP population (PP2) includes only patients for whom the measure of serum ferritin is available at baseline and after 1 year treatment.

For the secondary efficacy evaluation assessed as non-inferiority of DPF to DFX in terms of successfully chelated patients according to cardiac MRI T2* the PP population (PP3) includes only patients for whom the measure cardiac MRI T2* is available at baseline and after 1 year treatment.

Safety population

The population for the safety and tolerability analysis will include all patients having received at least one dose of study medication.

PK and PKPD population

The population for the pharmacokinetic and subsequent exploratory analyses (e.g. correlation between systemic exposure and ferritin levels) will include patients who have received the investigational drugs throughout the duration of the study (i.e., 1 year) and have had a blood sample collected for the assessment of drug concentrations in plasma.

11.3 Data Analyses

Data will be summarized with respect to demography and baseline characteristics, efficacy measurements, safety observations and measurements, health care resource utilization and patient global assessments. In addition, subgroup analyses will be performed by age group following the age ranges provided in the ICH Topic E11 guideline, and in details children (two classes 1 month – 5 years; 6-11 years) and adolescents (12- <18 years).

11.4 Demographic characteristics

Demographic characteristics will be summarized by treatment group using mean, standard deviation, median, percentiles for continuous variables and frequencies for categorical variables.

11.5 Study medication

Drug exposure will be summarized (using mean, standard deviation, median, percentiles) on a quarterly basis for each treatment arm and tabulated side-by-side. Any dose changes for safety reasons will be listed along with the cause.

11.6 Efficacy evaluation

Primary efficacy

The primary efficacy evaluation will be based on a treatment success rate defined in Section 4.3 Primary endpoint. The primary analysis will be based on the PP1 population.

In addition, an ITT analysis will be performed to corroborate the findings. If no composite endpoint is estimable at 1 year treatment (unavailability of serum ferritin and/or MRI determination either at baseline or after 1 year treatment), the subject is considered a treatment failure in the ITT analysis.
Non-inferiority will be assessed based on the two sided 95% confidence interval [δL, δU] of the difference $\delta = p_1 - p_2$, being p_1 and p_2 the proportion of success in the n_1 and n_2 patients randomised to DFP and DFX arms, respectively. Non-inferiority will be claimed if δL is greater than -0.125.
The two sided 95% confidence interval for δ will be estimated based on asymptotic normal approximation for the difference of two binomial probabilities as follows:

$$(p_1 - p_2) \pm Z_{1-\alpha/2}\sqrt{Var(p_1 - p_2)}$$

where Z_γ is the γ^{th} percentile of the standardised normal distribution and

$$Var\,(p_1 - p_2) = p_1(1-p_1)/n_1 + p_2(1-p_2)/n_2$$

If non-inferiority of DFP to DFX is established based on the PP1 population and the confidence interval for the null hypothesis of non-inferiority based on the ITT population is similar or the percentage of success for DFP is greater than that of DFX in magnitude, the hypothesis that DFP is superior to DFX in terms of the defined success criteria will be tested at the one-sided alpha level of 0.025. Superiority testing will be based on the ITT population. The rationale for superiority is justified by the known beneficial effects of DFP at the cardiac level.

Secondary efficacy

Efficacy measured through serum ferritin levels

Serum ferritin will be analysed as secondary measure of treatment efficacy. Serum ferritin is a well validated and clinically widespread surrogate measure of iron load, highly correlated with iron in the liver. It represents an easy to assess parameter in the paediatric population.

Serum ferritin will be tested in terms of quantitative variable as part of the composite endpoint measurable in the entire experimental population. The purpose of this analysis is to clarify the interpretation of the primary composite endpoint and hence no adjustment for multiplicity will be considered. The population for this analysis is the PP2. ITT analysis will be used to corroborate the findings.
Non inferiority of DFP to DFX will be tested considering a non inferiority margin of 400 ng/mL.
Non-inferiority will be assessed based on the two sided 95% confidence interval [δL, δU] of the difference $\delta = m_1 - m_2$, being m_1 and m_2 the mean difference between baseline and end of treatment assessments of DFP and DFX, respectively, and n_1 and n_2 the numbers of patients randomised to DFP and DFX arms. Non-inferiority will be claimed if δL is greater than -400 ng/ml.
The two sided 95% confidence interval for δ will be estimated as follows:

$$(m_1 - m_2) \pm Z_{1-\alpha/2}\,\sigma\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

where Z_γ is the γ^{th} percentile of the standardised normal distribution and σ^2 is the pooled variance.

Serum ferritin trends over the 1 year period of treatment will be also investigated. A repeated measures analysis of variance model with treatment-group as main effect will be fitted. The H_0 of equal between group regression slopes will be tested by evaluating whether the interaction between the categorical factor (treatment group) and the repeated measure (monthly measures of serum ferritins) equals zero, i.e. no interaction. The rejection of the null hypothesis on the interaction term (treatment group*monthly ferritin measure) will be supportive of different trends between DFP and DFX arms. The ITT population will be used for this analysis. Handling of missing data for this analysis is described in Section 11.4.

Descriptive statistics for trends in subgroups of patients according to age classes will be also provided.

Efficacy measured through cardiac T2* MRI

In the last years, the role of cardiac MRI T2* in the management of patients affected by hereditary haemoglobinopathies has been highlighted. Findings are available for the adult population, more limited experience is reported in children. Despite the importance of early detection of cardiac siderosis, MRI is difficult to perform In the paediatric population and it is usually uninformative in younger children (namely less than 10 years) due to late iron accumulation in the heart.

As a consequence, cardiac MRI T2* will be analysed as additional secondary measure of treatment efficacy in the subgroup of patients (over 10 years) for which the scan is available. It will be analysed as binary variable (successfully/unsuccessfully chelated patient according to the criterion 4.3.1 in Section 4.3) as part of the composite endpoint as well as according to its quantitative nature.

Due to the paucity of paediatric data on cardiac MRI T2*, descriptive statistics will be calculated and used to support efficacy conclusions. Descriptive measures will be listed by visit and treatment and characterised by frequency and percentage or mean, standard deviation, median, and quartiles.

However, considering the importance of improving knowledge on iron overload at the heart level in the paediatric population, a test for non inferiority of DFP to DFX in terms of cardiac MRI T2* (successfully/unsuccessfully chelated patient according to the criterion 4.3.1 in Section 4.3 Primary endpoint) will be performed whenever MRI evaluation will be available in at least 60-70% of the evaluable population. See section 11.3 different scenarios (non inferiority margins and sample size) related to this secondary efficacy assessment. The population for this analysis is the PP3.

Efficacy measured through MRI liver iron concentration

Iron overload in the liver compartment will be assessed as additional secondary measure of efficacy. LIC changes within one year will be evaluated in terms of percentage of successfully chelated patients according to the success criterium described in section 4.4.1 Secondary endpoints. LIC absolute values will be also analysed.

Considering the target population of the study, it is likely that patients undergoing cardiac MRI T2* will be also those patients able to perform R2 scan for LIC assessment. LIC measures are hence expected to be available in a subgroup of the experimental population. As a consequence LIC estimates as additional secondary measure of efficacy will be analysed only in terms of descriptive statistics. Descriptive measures will be listed by visit and treatment and characterised by frequency and percentage or mean, standard deviation, median, and quartiles. The population for this analysis is the PP3.

11.7 Safety evaluation

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. ECG, vital signs, and special tests) will be considered as appropriate.

AEs will be summarized by presenting, for each treatment, the number and percentage of patients having any AE and having an AE in each body system. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g. ECG or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. If suitable summary statistics will be presented. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration. Further details will be specified in the analysis plan provided prior to data base lock.

A summary of clinically relevant toxic events, i.e., adverse events that are serious, adverse events or laboratory tests that lead to change of dose of study medication or discontinuation from study medication will be provided.

11.8 Pharmacokinetic evaluation

The objective of the pharmacokinetic analysis is to evaluate the influence of potential covariates (e.g., subject's demographics, disease status and concomitant medications) on the parameters of interest.

The data collected in this study will be enriched with data obtained during the DEEP-1 DFP pharmacokinetic study. Covariate effects will be assessed using non-linear mixed effects modelling. During each step in the covariate model building process, statistical diagnostic tools will be used to evaluate model performance.

11.9 Exploratory PKPD analysis

The main objective of this analysis is to explore whether a correlation can be established between treatment response and steady-state concentrations of the investigational drugs. Therefore, pharmacokinetic data collected for DFP and DFX will be analysed in conjunction with the primary pharmacodynamic endpoints (ferritin and MRI). Data will subsequently be modelled using nonlinear mixed effects modelling, as implemented in the software NONMEM (Icon Development, MD, USA).

11.10 Health Care Resources Utilisation

The level of resource utilization in each treatment group will be summarized but will not be subjected to inferential statistics.

11.11 Interim analyses

No interim analyses are planned for this study. Two times a year a safety update will be provided to an independent Data Safety Monitoring Committee (DSMC), reviewing, evaluating and categorizing safety findings in the context of the entire program of paediatric registration trials for DFP.

11.12 Sample Size and power considerations

Primary efficacy objective

Assuming type I and type II errors of 0.025 and 0.20, respectively, and a one-sided test, and under the assumptions that the expected proportion of subjects declared treatment successes in the DFX arm is 65%, and the expected proportion of subjects declared treatment successes in the DFP arm is 67.5% a sample size of 310 subjects, randomized in a 1:1 ratio to DFP or DPX will yield 80% power to demonstrate non-inferiority of DFP versus DFX. Taking into account a possible dropout rate of about 20% a total enrolment of 388 patients aged from 1 month to less than 18 years are expected to be included in the trial.

Secondary efficacy objective

Sample size requirements for the secondary efficacy objectives (non-inferiority in terms of ferritin levels and cardiac MRI T2*) are provided in the following.

Based on published literature, testing for non-inferiority is appropriate also when comparing DFP to DFX efficacy in terms of serum ferritin levels. In this case, considering a hypothesis testing on the continuous measure, a non inferiority margin of 400 ng/ml is considered a reliable estimate of the true allowed maximum difference between the IMPs in order to assume DFP to be non-inferior to DFX in controlling iron overload in patients affected by hereditary haemoglobinopaties. The standard deviation of the differences is available by pooling findings from paediatric studies conducted in Europe and outside (El Alfy M et al., 2010), and a reliable and conservative estimate can be 1000 ng/mL.

On these assumptions, 310 evaluable patients are sufficient to provide at least 90% power to demonstrate non inferiority of DFP to DFX, assuming a type I error of 0.025 and a one-sided test.

When considering efficacy in terms of cardiac MRI T2*, less reliable estimates of treatment efficacy are available, especially in the paediatric population. However, there are no reasons for not assuming at least a non inferiority of DFP to DFX, considering also the known beneficial effects of DFP at the cardiac level.
Based on the limited published figures of cardiac MRI T2* in the paediatric population and taking into account adult data, some plausible scenarios of sample sizes and related powers are provided in the following **Table 7**, assuming a type I error of 0.025 and a one-sided test. Detailed power curves will be provided in the statistical plan.

Table 7. Sample size and power on cardiac MRI T2* (percentage of successfully chelated patients)

DFX/DFP Success (%)	65/70	65/70	70/75	70/75
Non inferiority margin (%)	-12.5	-10	-12.5	-10
Power (%)	80	75	80	75
n (per group)	112	135	102	123

On these calculations, a test for non inferiority in terms of percentage of successfully chelated patients according to the criterion 4.3.2 as defined in Section 4.3 Primary endpoint is considered feasible and supported by an adequate power whenever cardiac MRI T2* is available in about 60-70% of the evaluable population.

11.13 Handling of missing data

A negligible amount of missing data is expected in this study because the patient population under study (patients affected by haemoglobinopathies requiring chronic transfusion and chelation therapy), and their parents, are accustomed to routine close monitoring in clinical visits, are used to frequent lab tests and comply with uncomfortable examinations (MRI), and are generally willing to participate in trials that may lead to increasing the availability of treatments. Moreover, the estimated treatment effect is not expected to be importantly biased in favour of the experimental treatment due both to the choice of the comparator and of the primary endpoint.
DFX is an oral chelator as DFP, and its compliance is expected to be comparable to that of DFP, or even better taking into account the once a day administration.
The completeness of the data that will allow the estimate of the primary endpoint (percentage of successfully chelated patients) is expected to be high due to the type of patients and condition.
Finally, patients who prematurely discontinue the trial for any reason will be considered treatment failures.

Assuming the worst scenario for incomplete data in order to provide conservative estimates for the trial results, the imputation of missing data will only apply to missing data because of a missing visit. This will affect the trend analysis for the secondary evaluation on serum ferritin levels. In this case, Linear Mixed Models (LMM) will be used as imputation method for missing data.

12. DATA COLLECTION AND RETENTION

Designated investigator staff must enter the information required by the protocol into the CRF using dedicated computer loaded with fully validated software that conforms the requirements for electronic data capture. Automatic validation programs check for data discrepancies in the electronic CRF and, by generating appropriate error messages, allow modification or verification of the entered data before transfer to Sponsor via a secure internet link. The Principal Investigator must certify that the data are complete and accurate and later receives a CD-ROM or paper copies of the patient data for archiving at the investigational site. All electronic CRFs sent to Sponsor by investigational sites are reviewed upon receipt for any SAEs.

Data on subjects collected on CRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the patient sequential number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the Sponsor and the Investigator are bound to keep this information confidential.

The Investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, ECGs, etc., and keep a copy of the signed informed consent form. All information on CRFs must be traceable to these source documents in the patient's file.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations.

13. SITE MONITORING

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor or CRO representative will review the protocol and the CRFs with the investigators and their staff. During the study the monitor will visit the site regularly, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrolment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the field monitor during these visits.
The Investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study centre. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the case report forms are performed according to the study-specific monitoring plan.

14. AUDITING PROCEDURES

Audits of clinical research activities in accordance with internal Standard Operating Procedures will be conducted by the Sponsor or CRO to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the Principal Investigator must inform the Sponsor immediately that this request has been made.

15. QUALITY ASSURANCE

Data items are entered directly into the study database or indirectly from source data documents by designated and trained investigator staff using single data entry with electronic verification. Sponsor staff reviews the data for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query system which provides an automatic audit trail of the corrections made by designated investigator staff.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the Sponsor as specified in the SPM.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Trial Coordinating Investigator and the Data Manager.

16. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE) REPORTING

According to ICH E6 Guideline (Good Clinical Practice, GCP), both Investigators and Sponsor follow specific **procedures when notifying and reporting adverse events/reactions in clinical trials.**

The Principal Investigator or qualified site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of Investigational Product and until the follow-up contact. Medical occurrences that begin prior to the start of investigational product but after obtaining informed consent should be recorded separately from the Medical History/Current Medical Conditions CRF.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to 30 days from last dose or study related invasive procedure. All SAEs will be recorded and reported to Safety Contact (SC) within 24 hours after the Investigator has become aware of the event, as indicated in Section 16.3.

16.1 Definitions

In this trial protocol the definitions reported in **Table 8** apply according to the Art.2 of the Directive 2001/20/EC.

Table 8. Definitions

TERM	DEFINITION
'**Adverse Event**' (AE)	any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment[A]
'**Adverse Reaction**' (AR)	all untoward and unintended responses to an investigational medicinal product related to any dose administered
'**Serious Adverse Event** or **Serious Adverse Reaction**' (SAE or SAR)	any untoward medical occurrence or effect that at any dose: ▪ results in death ▪ is life-threatening[B] ▪ requires hospitalisation or prolongation of existing hospitalization[C] ▪ results in persistent or significant disability or incapacity[D] ▪ is a congenital anomaly or birth defect ▪ other medically important/clinically significant events[E]
'**Unexpected Adverse Reaction**' (UAR)	an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)

[A] *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.*

[B] *The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*

[c] *In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.*
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

[D]*The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*
[E]*Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic reaction, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.*Events meeting the definition of an AE include:

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

16.2 Method of Detecting AEs and SAEs

At each study visit, care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?" **or** "How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" **or** "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" **or** "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

16.3 AE and SAE evaluation

I. Assessment of Severity (i.e. intensity)

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- ***Mild***: an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- ***Moderate:*** an event that is sufficiently discomforting to interfere with normal everyday activities.
- ***Severe:*** an event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

II. Assessment of Seriousness

When an AE/AR occurs the Investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in **Table 8**. If the event is serious, then an SAE form must be completed and the SC notified.

III. Assessment of Causality

The Investigator must assess the causality of all events/reactions in relation to the trial therapy using the definitions in **Table 9.**

There are 5 categories: unrelated, unlikely, possible, probable and definitely related. The causality assessment is unrelated or unlikely to be related the event is classified as an AE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a AR. If a drug is possibly related to an AE, this should be noted on the follow up form.

Table 9. Causality Assessment

Relationship	Description	Type
Unrelated	There is no evidence of any causal relationship	AE
Unlikely	There is little evidence to suggest there is a casual relationship (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant treatment).	AE

Possible	There is some evidence to suggest there is a casual relationship (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant treatment).	AR
Probable	There is evidence to suggest there is a casual relationship and the influence of other factors is unlikely.	AR
Definitely related	There is clear evidence to suggest there is a casual relationship and other possible contributing factors can be ruled out.	AR

IV. Assessment of Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event. If a SAR is assessed as being unexpected it becomes a SUSAR. The definition of an unexpected adverse reaction (UAR) is given in **Table 8** and is one not previously reported in the current SmPC (for the authorized product, namely deferasirox) or IB (for the IMP, deferiprone).

16.4 Reporting

Investigator Responsibility

All SAEs must be reported by the Investigator to SC on a SAE form within 24 hours of the investigator being aware of the event.

Notification procedure:

I. The SAE form must be completed by the Investigator or by trained authorised person with the right to access in the e-CRF. The responsible investigator or the trained authorised person should complete the online "SAE section" of the e-CRF, print it in a pdf format and then fax it to the Safety Contact as soon as possible. The initial report shall be followed by detailed reports as appropriate. Even if the Investigator has minimal information to include in the initial report it is important that he should always make an assessment of causality for every event prior to the initial transmission of the SAE data. The Investigator may change his/her opinion of causality in light of follow-up information and then sending the SAE form as follow up, amending the SAE data collection system accordingly.

II. Send the SAE form by fax to the SC.

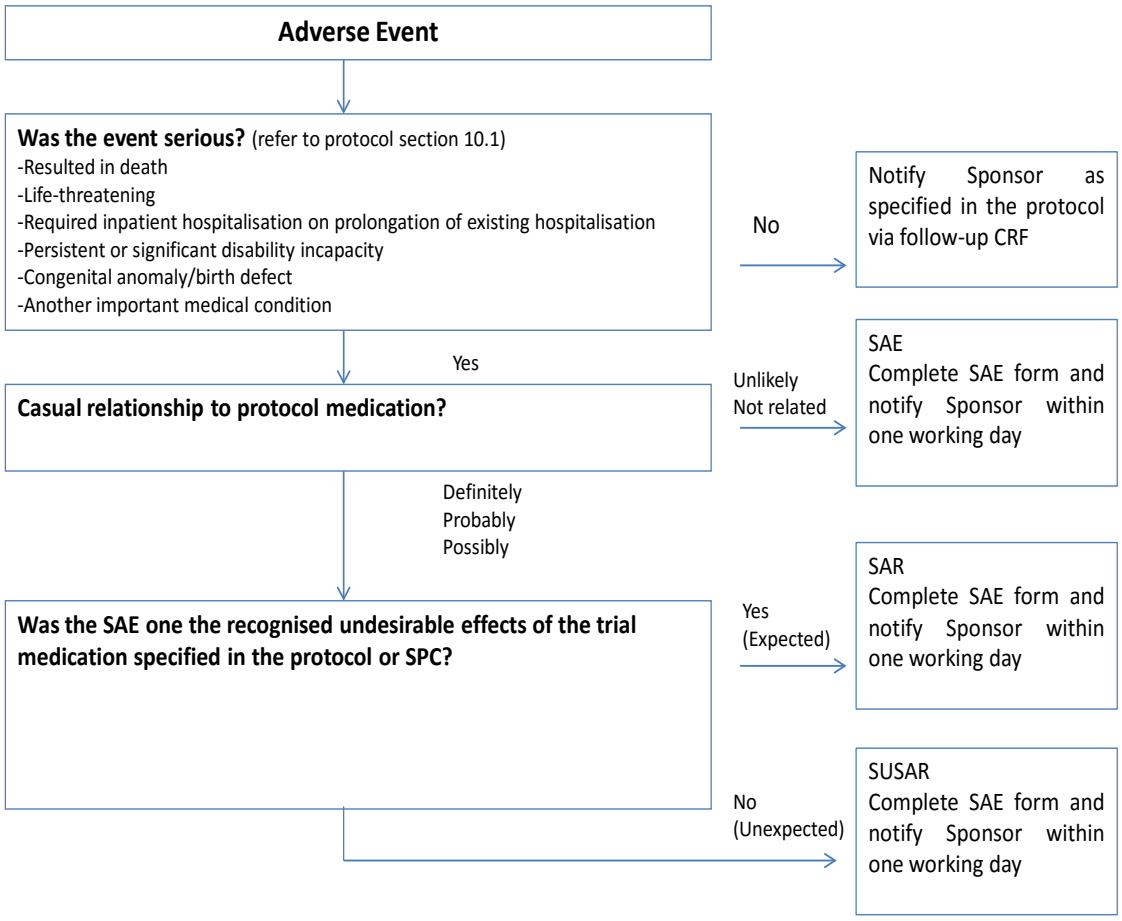
III. Follow-up: patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form in the "SAE section" of the e-CRF, by adding a Follow up form to the Initial Form. The Follow up form shall be printed in pdf format and sent by fax to the Safety Contact as information become available. Extra annotated information/or copies of test results may be provided separately. The patient must be identified by trial number and date of birth only. The patient's name should not be used on any correspondence.

Sponsor Responsibility

The Sponsor will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IEC/REB and Investigators. The Sponsor will also assure all Investigators are informed of any safety issues that arise during the course of the trial.

The modality by which adverse experience data are communicated by the Sponsor to study drug MAH or producer (as appropriate) are defined in an *ad hoc* agreement.

Figure 3. Safety reporting flowchart



The telephone and fax numbers of the SC are listed in the Investigator folder provided to each site.

16.5 Instructions for rapid notification of pregnancies

Each pregnancy, occurring in a participating female patient or partner of participating male patient that started during the study must be reported by the Investigator to the Sponsor within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up as well as any SAE experienced during pregnancy

must be reported on the SAE Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or new born complications and their relation to the Sponsor study drug (or therapy).

16.6 Instructions for rapid notification of Neutropenia

In this protocol all neutropenia, defined as ANC < 1500/mm^3 (confirmed in two consecutive measurements), irrespective of their severity or seriousness, will follow the procedure for SAE notification and must be reported by the Investigator to the Sponsor within 24 hours of learning of their occurrence according to the procedure described in Section 16.4 Reporting.

17. DATA SAFETY MONITORING COMMITTEE (DSMC)

The study will be conducted under the supervision of an independent DSMC. All DSMC members have extensive experience in either paediatric clinical trials and/or management of haemoglobinopathies. The DSMC is responsible for the ongoing review of a clinical trial and for making recommendations concerning the continuation, modification, and termination of the trial. Details of the DSMC membership, meeting schedule, and data review and analysis will be documented in the DSMC Charter.

18. HUMAN SUBJECTS

18.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) /Research Ethics Board (REB)Review

Ad hoc consent and assent form will be submitted to patients and their legal representatives before enrolling in the study. These forms have been developed in the context of the DEEP Project and have been submitted to the revision of the DEEP IEC according to the current National and European ethic rules also taking in to account the Convention on Human Rights and Biomedicine (Oviedo, 4.IV.1997), its Additional Protocol concerning Biomedical Research (Strasbourg 25.I.2005). Three different assent forms have been developed taking into account different age groups that include children <6 years, 6 - 10 years and >10 years.

A signed and dated statement that the protocol and the informed consent forms have been approved by the IRB/IEC/REB must be given to the Sponsor before study initiation.

Disclosure and Confidentiality

Study procedures are compliant with the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (Strasbourg, 28.I.1981). All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the patient sequential number to maintain subject confidentiality. All records and study documents provided by the Sponsor (protocols, investigators' brochures, CRFs and other material) will be kept in a locked file cabinet. All computer entry and networking programs will be done using patient sequential number only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the EC, the sponsor, or the sponsor’s designee.

By signing the protocol, the investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. The information provided by the Sponsor to the investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

18.2 Study Modification/Discontinuation

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Sponsor and the Trial Coordinating Investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centres, and, in some countries, by the regulatory authority. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. an addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by the Sponsor in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons the Sponsor should be notified and the IRB/IEC/REB at the centre should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each centre must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labelling of study drug.

19. PUBLICATION OF RESEARCH FINDINGS

The Sponsor recognizes the right of the individual Centre of utilizing data derived from the study for teaching purposes, communication at congresses and scientific publications. As such, the Sponsor has no objection to publication by the Centre of any information collected or generated by the Institution. However, to ensure the accuracy and scientific value of the information, while preserving the independence and accountability of the Centre and to maintain the confidentiality of the information, only cleared, checked and validated data will be used. To this effect, it is essential that the Centre provides the Sponsor an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.
For this purpose, the Sponsor shall be provided with the draft of any publication or release or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) and will have at least sixty (60) days to review and comment such draft before they are submitted for publication or otherwise disclosed, and, if necessary, to delay publication in order to protect the confidentiality or proprietary nature of any information contained therein. If Confidential Information is to be disclosed, proposed publications or presentations will be delayed until the appropriate patent applications and/or legal documents of a similar nature have been filed.

Publications will be managed according to the Rules set by the European Commission within the Framework Programme 7:

a) All publications shall include the following statement: "The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 261483".
b) An electronic copy of the published version or the final manuscript accepted for publication of a scientific publication has to be delivered to the DEEP Consortium in order to allow the latter to deposit such document in an institutional or subject-based repository at the moment of the publication.
c) The Institution is required to make its best efforts to ensure that scientific articles become freely and electronically available:
   I. immediately if the an electronic version is also available free of charge via the publisher, or
   II. within 6 months from publication.

20. BENEFIT RISK ASSESSMENT

Risks

By participating in this research it is possible that the patients may experience some distress, even if the procedures foreseen in this trial are quite similar to those required for a well management of patients affected by hereditary haemoglobinopaties requiring chronic transfusions. Patients are submitted monthly to blood samplings and have to undergo MRI examinations three times during the 1 year period of treatment (at baseline, at month 6 and at month 12). The duration of MRI tests is higher at baseline and at the end of treatment since both cardiac and liver compartments have to be investigated.

Every measure to prevent distress and discomfort will be put in place. Blood samplings will be performed with butterfly needles at least in younger children or in children showing anxiety and distress. Moreover, monthly sampling will be planned to coincide as much as possible with the day of blood transfusion to which the patient must regularly undergo for the underlying disease.
Concerning MRI, for ethical reasons, the examinations are foreseen only in children for whom sedation is not required. Besides distress related to the procedure, some discomfort may however be experienced by patients referring to clinical centers not equipped for performing MRI examinations. These patients will be moved to the closest centre able to perform the MRI scan. Even if the costs for these displacements are covered by the study, patients may found some logistics difficulties impacting on their life and health.

Finally, during the course of the study patients could experience AEs following the use of both the experimental drug and the active comparator. Every effort will be made both by the medical investigator and by the sponsor to ensure appropriate monitoring of safety/tolerability and suitable measures will be put in place to handle and mitigate AEs.

Benefits

Patients enrolled in this trial are offered the opportunity to benefit from an oral chelator to treat their iron overload, thus improving treatment compliance and ultimately treatment efficacy.

For children randomized to the experimental arm, the use of a new strength (80mg/mL) of the currently marketed DFP oral solution will allow a more precise administration of the right dose according to the weight to the child. For those patients randomized to the control group the costs for the comparator

(deferasirox) are covered by the trial in those countries in which no facilities are provided, thus allowing children to benefit from the oral chelating agent.

Specific benefits are expected for a particularly vulnerable subgroup of the experimental population, namely children from 1 month to less than 6 years. These patients will be enrolled in the trial only after the availability of results identifying the most suitable dose and dosing regimen of DFP in this age group as derived from the PK study (Study DEEP-1, EudraCT n. 2012-000658-67).

21. REFERENCES

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Annex 1. Exjade SmPC 125 mg, 250mg, 500 mg
Annex 2. Child Health Questionnaire (CHQ-PF28)